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HUMAN VARIABILITY IN SUSCEPTIBILITY TO TOXIC CHEMICALS -- I. NONCARCINOGENS

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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16. ABSTRACT

The tenfold "safety" factor traditionally used to guard against human interindividual differences in susceptibility to toxicity is not based on human observations. Some support for a tenfold dose-reduction is based upon the distribution of probit slopes from acute toxicity in animals. Although human data is preferable, epidemiologic data are unlikely to have precise exposure measurements. To study human interindividual variability we used papers from the recent pharmacological literature to construct a data base of individual measurements of key pharmacokinetic parameters for specific substances (mostly drugs). The parameters studied, elimination half-lives, maximal blood concentrations and area under the curve (AUC) of blood concentrations are only components of overall susceptibility to toxic agents, and do not include variability parameters that would affect exposure and response, nor from age or illness. 72 of the 101 data sets studied were positively skewed, indicating that the distributions are generally closer to log-normal distribution than a normal distribution. There are greater amounts of interindividual variability in data sets where AUC was measured. This component of variability in humans did not appear to be substantially less than the total variability observed in animal data available for comparison.

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PREFACE

The Environmental Criteria and Assessment Office of the Office of Health and Environmental Assessment has prepared this report for use by the Office of Solid Waste in evaluating the uncertainties in risk assessment procedures. These risk assessment procedures are used for deriving Reference Doses for noncarcinogenic chemicals or risk levels for carcinogenic chemicals that may be present in hazardous wastes. This report is limited to noncarcinogens. A second phase of this project will result in a similar report on factors contributing to inter-individual variability in response to carcinogens.

The literature was searched for studies from 1979-1985 that contained human data on inter-individual variability in factors relating to sensitivity to toxic substances. The goal was to ascertain the likely range of sensitivity in humans based on a preliminary assessment of available data on one of the several potential causes.

Each experiment was examined and the associated bibliographic information was summarized in a data base that can be accessed by interested researchers. The report also explains the structure and terminology of the data base.

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SUMMARY

This report summarizes an initial effort to assemble human data of the variability in key pharmacokinetic parameters in a form that can be applied to the quantitative assessment of human risk from toxic chemicals. From the standpoint of the risk assessor, differences among individuals mean that population risk vs. dose will be systematically different from the risk that would be faced at different doses by any individual within the population.

Papers from the recent literature (most from 1979-1985) were selected for possible study if they contained individually distinguishable human data for at least five people on parameters related to susceptibility to toxicants. The selected papers were first sorted according to the kind of parameters measured. Papers containing data on pharmacokinetic parameters in normal healthy adult populations were used for the present analysis. This restriction implicitly has limited the type of variability captured in two ways: (1) "exposure" and "response" type variability are excluded; and (2) most variability that comes from age, pathology, or other special situations (such as pregnancy, interacting exposures) is also excluded. However, the selection criteria used do allow the data to be readily compared with observations of interindividual variability in rats as observed in acute oral LD_{50} experiments described by Weil (1972), and with lethal toxicity probit risk equations as developed for the U.S. Coast Guard's "Vulnerability Model." The Weil data have recently been used as support for the traditional 10-fold safety factor for interindividual variability that is used in the computation of "Acceptable Daily Intake" values (Dourson and Stara, 1983).

As presumed by both the "Vulnerability Model" probit risk equations and the Dourson-Stara/Weil analysis, the basic forms of the observed distributions of pharmacokinetic parameters related to individual susceptibility appear to be better described as log-normal than as normal distributions. Fully 72 of the 101 data sets examined here were found to have a positive value for skewness when the data were not logarithmically transformed. However, analysis of kurtosis statistics for the distributions after logarithmic transformation suggested that the data sets may often be flatter in the middle and heavier in the tails than would be expected for truly log-normal distributions. One possible explanation for this is that there may often be some degree of bi- or multimodality in the data.

Elimination half-lives and maximal blood concentrations both were found to have median values of $\log_{10}$ geometric standard deviations somewhat over 0.11* -- not very different from the total geometric standard deviation of susceptibility of 0.0934 - 0.114 assumed for chlorine and ammonia in the Coast Guard's "Vulnerability Model" (Eisenberg and Lynch, 1975). There seems to be some tendency toward greater amounts of interindividual variability in data sets where AUC (Area Under a Curve of blood concentration by time) or steady-state blood concentrations were the measured parameters. In this case the median $\log_{10}$ geometric standard deviation is about 0.145 and three of the 20 data sets are over 0.3 (compared with none of 61 data sets over 0.3 in the case of $T_{1/2}$). Of those parameters studied, AUC has the greatest relevance for representing interindividual pharmacokinetic differences for effects with linear

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*In the antilog form that is often used to express geometric standard deviations, a $\log_{10}$ geometric standard deviation of 0.11 would correspond to about 1.29 (because $10^{0.11} = 1.29$).

nonthreshold dose response relationships. Peak blood concentrations are more directly relevant for acute toxicity.

A similar result was obtained when comparisons were made between our human pharmacokinetic data and the results using rats reported by Weil (1972). The interindividual variability in specific pharmacokinetic parameters for the 49 agents studied in groups of normal healthy adult humans does not depart markedly from the distribution of <u>total</u> variability in susceptibility to acute lethal effects of chemicals in groups of rats (Weil, 1972). Where Weil found that about 14% of the rat data sets had $\log_{10}$ geometric standard deviations of over 0.25, the proportion of chemicals showing this degree of interindividual variability in specific pharmacokinetic parameters was approximately 5% for elimination half-lives (2/44), 20% for AUC measurements (3/15), and 8% for peak blood concentrations (1/12). One of four observations in a miscellaneous set of "other" parameters was also above this level of indicated interindividual variability.

The parameters studied in humans, however, are only <u>components</u> of overall susceptibility to toxic agents and do not include contributions from variability in exposure- and response-determining parameters. The data also include no contribution to variability from diseased or other special subpopulations and it is these types of sensitive subpopulations that have often been of major concern for standard setting under environmental laws such as the Clean Air Act.

The numbers of chemicals and human parameters summarized to date are clearly small, both relative to the available human literature and to the animal data set compiled by Weil (1972). Based on the limited survey of the literature undertaken in Phase I, it seems likely that the overall data base

assembled here could be expanded 3-fold to 6-fold with a relatively straightforward extension of the present work. Future work should also clearly include studies of "exposure" and "response" parameters, and studies in patient and various "special" subpopulations likely to depart significantly from average susceptibility among normal healthy adults. Further, it is important to document whether instances of relatively greater apparent variability are associated with different structural categories of chemical agents, different modes of administration, different metabolic pathways, age-restricted vs. not age-restricted population samples, and other study characteristics. Finally, the lessons from these different analyses should be integrated into predictive models of human inter-individual variability as an aid for quantitative human risk assessment for toxic chemical exposures.

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1. INTRODUCTION

This paper resulted from an initial effort to assemble human data on variability in key pharmacokinetic parameters in a form that can be applied to the quantitative assessment of human risk from toxic chemicals. Individual biological variability among members of the same species is a fact of life in experimental biology and medicine. Whether produced by genetic differences, differences in age, differences in previous exposures, or other factors, different individuals often react differently to what appear to be similar challenges from biologically active chemicals. It is in recognition of these factors that epidemiologic and clinical studies routinely subclassify their subjects by age, sex, and disease state -- to control for their roles and measure their effects.

From the standpoint of the risk assessor, differences among individuals mean that <u>population</u> risk vs. dose will be systematically different from the risk that would be faced at different doses by any <u>individual</u> within the population. For example, for types of effects that have threshold-type dose response curves, individual risk is essentially zero below the threshold and rises sharply to 100% at the threshold level and above. In this case, variability among individuals in their thresholds for response produces a <u>population</u> dose response curve in which the incidence of effects rises more gradually with increasing dose as increasing percentages of the population receive doses that exceed their individual thresholds. If there is a continuous normal or log-normal distribution of susceptibility (thresholds) in the population, the population dose response curve will take on the familiar S-shape -- rising gradually at low doses, increasing in slope to an inflection point at about a 50% incidence of response, and then flattening out at high doses as close to 100% of the available population is affected.

Clearly, defining just how variable human populations are likely to be is a central issue in performing quantitative risk assessments for effects with mechanisms that are likely to produce thresholds when viewed from the standpoint of individuals. (Variability can also be important in affecting the shapes of population dose response curves with non-threshold type mechanisms, but it is the central feature of importance in determining population risk for threshold-type effects.)

At present, standard toxicological practice within EPA and other agencies such as FDA and WHO is to use a 10-fold safety factor to account for likely variability in susceptibility among individual humans. The origins of this classic rule of thumb are obscure. It is not clear whether it was originally based on an analysis of data at all, or if so, just what fraction of the human population was expected to be protected by the 10-fold rule. Recently, however, Dourson and Stara (1983) prepared an analysis that defends the 10-fold rule on the basis of observations in animals compiled by Weil (1972). Weil (1972) presents a histogram of probit slopes from 490 determinations of acute lethality from single oral doses in rats. (Table 1 reproduces this data, as interpreted from the histogram.) Weil (1972) provides little description of this data set -- whether or not it represents 490 different chemicals, what kinds of chemicals are covered, and what strain(s) of rat were used. Nonetheless it does provide a starting point for discussion of the magnitude of within-species variability and comparison with observations of variability in susceptibility in humans. Based on the Weil (1972) data, Dourson and Stara (1983) observed that 92% of chemicals appear to have probit slopes greater than 3. This implies that in that proportion of cases a 10-fold lowering of dosage will span at least three standard deviations in susceptibility -- if a dose of 1 unit of the chemical produces 50% mortality, a dose of 0.1 unit would be expected to produce

TABLE 1

Frequency Distribution of Log-Probit Dose Response Slopes Observed in Oral LD_{50} Determinations in Rats

Log Probit Slope[a]	Implied Log Standard Deviation of Susceptibility[b]	Number of Observations (Chemicals?)	Cumulative % of Observations
1.4-2	0.5-0.71	7	1.4
2-4	0.25-0.5	60	13.7
4-6	0.1667-0.25	90	32.0
6-8	0.125-0.1667	97	51.8
8-10	0.1-0.125	71	66.3
10-12	0.085-0.1	57	78.0
12-16	0.0625-0.085	53	88.8
16-22	0.045-0.0625	34	95.7
22-30	0.0333-0.04545	13	98.4
30-65	0.0154-0.0333	8	100
	TOTAL	490	

[a]Standard deviations of the distribution of susceptibilities per 10-fold change in dose.

[b]This is the reciprocal of the probit slopes in the first column.
Source: Weil, 1972

0.13% mortality, assuming a log-normal distribution of susceptibility. Dourson and Stara (1983) caution, however, that

> ...these probit, log-dose slopes are gathered on laboratory rats which are generally expected to be less heterogeneous in response to the toxicity of a contaminant when compared to the human population. Greater heterogeneity in response is associated with lower slopes and correspondingly greater dosage reductions [required for the same degree of protection].

Another point of departure for discussion of the magnitude of human variability is some implicit assumptions of human variability that are built into current risk assessment models for predicting the proportion of people that would be killed by various doses of acute toxic agents released from large facilities in catastrophic accidents. For example the "Vulnerability Model" developed by Enviro Control Inc. for the U.S. Coast Guard (Eisenberg et al., 1975) uses the following equations for the lethality risk of chlorine and ammonia:

Chlorine: Probit of risk = $-17.1 + 1.69 \ln(C^{2.75}T)$

Ammonia: Probit of risk = $-30.57 + 1.385 \ln (C^{2.75}T)$

where the air concentration, C, is in ppm and the time, T, is in minutes. On rearrangement and conversion of the natural logarithms to $\log_{10}$, the coefficients that multiply the $\ln (C^{2.75}T)$ terms in these equations imply $\log_{10}$ geometric standard deviations of .09345 and .1140, respectively, (or, in the antilog form that is often used for expression of geometric standard deviations, 1.24 and 1.3).

How does actual human variability compare with the variability suggested in the Weil data set and the chlorine probit lethality risk equation? This paper is an initial effort to begin the process of assembling available human data on parameters related to susceptibility to toxic chemicals in a

form that is conducive to making those comparisons. Before proceeding, however, it may be helpful to set forth some formal definitions of terms:

Potency -- The dose of a chemical that produces a standardized response. It is important to hold the response constant and define potency in terms of dose because often standard toxicological response parameters are not linear functions of dose. For example LD_{50} (the dose of chemical that kills 50% of a test population of animals) is a potency measure because it describes what amount of chemical is needed to produce this generally non-linear effect. It can be compared straightforwardly among chemicals where a measure based on the percentage of animals killed per unit dose would be misleading.

Susceptibility -- The reciprocal of the dose that is needed to produce a standardized response in an individual or population. Thus, an individual whose threshold for bronchial irritation from SO_2 was 0.5 ppm would be said to be 10 times as susceptible as an individual who required 5 ppm to produce the same response.

Susceptibility Component -- A parameter, measureable in individuals of a population, that is likely to be directly related to individual susceptibility for some specific type of toxicity when other relevant parameters are held constant. For example, an elimination half-life (generally, the time it takes for half of a chemical to be eliminated from blood) is a susceptibility component because, other things being equal, the level of chemical accumulated in the body on a chronic continuous dosage regimen will be directly related to the elimination half-life.

Because susceptibility is expressed as the reciprocal of a dose, whereas chemical potency is directly related to a dose, the probit slopes used for potency determinations (and recorded in the first column in Table 1) are really the reciprocals of measures of variability in susceptibility, as shown in the second column of Table 1. Thus a log probit slope of 2 implies a log-normal distribution of individual susceptibility with a logarithmic standard deviation of 0.5. (That is, for a chemical where the median susceptibility of a population was 1, 95% of individuals would be expected to have susceptibilities between $1/10^{(2 \times 0.5)}$ and $1 \times 10^{(2 \times 0.5)}$, or between 1/10 and 10. Slightly less than 2.5% of such a population would be more than 10 times as susceptible (respond at 1/10th the dose) as the median individual.

2. SELECTION OF PAPERS/PARAMETERS FOR REVIEW

Papers from the recent literature (most from 1979-1985) were selected for possible further study if they contained individually-distinguishable human data on parameters related to susceptibility to toxicants for at least five people. Papers with only summary statistics (e.g., means and standard deviations) were not included. Papers containing data on parameters of principal relevance to carcinogenesis (i.e., DNA repair) were deferred for study in another project.

In an initial search of papers from 1979 to 1983, 95 papers met these criteria (Table 2). Ten had exposure-related parameters (either behavioral factors, such as breathing rates, which would influence dose in the presence of a given concentration of a pollutant in an environmental medium, or observations of the concentrations of toxic substances in general population samples). The largest number of papers (75) consisted of papers with measurements of pharmacokinetic parameters (defined as parameters that affect tissue dose rate or dose X time per mg/kg of external dosage. These papers with pharmacokinetic data were further subclassified by the types of population studied:

(1) measurements in normal healthy adult volunteers,

(2) measurements in patient populations suffering from various medical conditions,

(3) measurements in occupational and other special subgroups.

Finally, 10 papers with potentially usable information on "response" parameters (differences in some biological response after controlling for blood or tissue dose) were identified. Table 2 summarizes the number of papers in these three categories cross-classified by the total sample size available for analysis.

TABLE 2

Distribution of Qualifying Papers
by Type of Parameter and Sample Size

Type of Parameter	Total Papers	Number of Papers By Total Sample Size					
		5-9	10-19	20-49	50-99	100-499	500+
Exposure	10		2	1		2	4
Pharmacokinetics							
Normal Vol.	49	19	16	7	3	4	
Patients	13	3	6	3		1	
Other/special	13	1	3	5	4		
Total Pharm.	75	23	25	15	7	5	
Response	10	4	2	3		1	
All Parameters	95	27	29	18	7	8	4

Although there was a minimum requirement for a sample size of 5, the papers for study were not further winnowed to select the papers with the largest numbers of individuals studied. In many cases the largest pharmacokinetic studies seemed to have been done to gather information about the frequency of single-gene abnormalities in drug metabolism (i.e., hydroxylation or acetylation of a test drug) and therefore could constitute an unrepresentative sample of all materials with measurements.

For our initial analysis we elected to focus on the cleanest, most easily-interpreted data -- the 49 papers that contained information on pharmacokinetic parameters in normal adult volunteers -- expanded to a total of 79 papers by a further search of the literature into 1985. A difficulty inherent in this approach is this initial analysis implicitly has limited the type of variability captured in two ways: (1) exposure and response type variability are excluded; and (2) most variability that comes from age (in most cases), pathology, or other special situations (such as pregnancy, interacting exposures) is also excluded.

In partial compensation for these limitations is the fact that an analysis based solely on normal volunteer data provides the most direct comparison with the animal data presented by Weil (1972). Experimental acute toxicity studies would normally be done in young healthy adult animals. However, it cannot be emphasized too much that the preliminary analysis in this paper does not capture what may well be substantial sources of individual variability in the diverse human population exposed to toxic agents. Ultimately it will be necessary to construct simulation models to adequately capture the influence of diverse sources of interindividual variability in the human population.

In studying the papers with pharmacokinetic data, the highest priority for analysis was given to three specific kinds of pharmacokinetic parameters that are likely to be particularly important in determining overall susceptibility for different kinds of adverse effects:

- Elimination half-lives ($T_{1/2}$) -- defined as the time required for a 2-fold decline in the concentration of the substance in some compartment (usually blood) after absorption is essentially complete. In general, the longer the elimination half-life, the higher the concentrations that will be attained in the body if exposure is continuous or repeated at a frequency that is short relative to the half-life. Therefore elimination half lives are likely to be key determinants of susceptiblity to toxicity from chronic continuous exposures. Often blood concentrations are observed to decline in two phases -- an initial "distribution" phase in which concentrations of the substance in some other body compartments come into rough equilibrium with the blood concentrations -- and a later phase in which the primary mechanisms of decline of blood concentration are metabolism or excretion. In such cases the half-life from the second phase (usually designated $T_{1/2\text{-beta}}$) was selected for analysis. When elimination rate data were given in the form of a first order rate constant, k, $T_{1/2}$ was calculated using the formula $T_{1/2} = (\ln 2)/k$.

- Area Under the Curve (AUC) of a plot of the plasma concentration vs. time after exposure -- This measure is the one that would be most directly relevant to the effective dose of a mutagen or carcinogen that acted by direct reaction with DNA. It has the additional virtue of integrating variability in the efficiency of absorption as well as metabolism/elimination, in contrast to $T_{1/2}$.

- Peak Concentration (C_{max}) in blood -- This is the measure that will usually be most directly relevant for representing effective dose in cases of acute toxicity from an isolated single exposure to a substance. Like AUC, it also integrates information about absorption -- in this case both the efficiency and dynamics of absorption.

One difficulty that was often encountered in analyzing information about AUC and peak concentrations was that the dosage was provided as some given weight of the substance (i.e., a 100 mg pill) without any information that allowed conversion of the dosage for individuals into mg/kg body weight. In such cases the data would reflect a complicating contribution from inter-individual differences in body weights, and not true differences in tissue dose per mg/kg external dose. Such papers were therefore excluded from the

analysis. Papers were also excluded if the parameters measured had an ambiguous or questionable relationship to actual susceptibility to toxic effects, such as urinary excretion of metabolites. Overall, 13 of the 79 papers were excluded because it was not possible to correct the data for body weight, 8 were excluded because they only provided urinary excretion data or some other parameter that proved too difficult to relate directly to susceptibility, and 4 others were excluded for miscellaneous reasons. Table 3 is a detailed listing of the excluded papers and the reasons for their exclusion. In the end 54 papers yielded usable quantitative information for analysis.

Volume of distribution was not analyzed because this parameter can influence susceptibility in either direction or have no effect, depending on the dynamics and mechanism of toxicity.

TABLE 3

Reasons for Exclusion of Specific Papers

First Author, Year	Chemical	Reason for Exclusion
Bryson, 1982 et al.	Disopyramide	Not possible to correct for body weight
Butler, 1982	Aspirin	Not possible to correct for body weight
Cooper, 1981 et al.	Desmethyl-imipramine	Not possible to correct for body weight, original data from cited paper needed.
Dahlstrom, 1982 et al.	Noscapine	Internal inconsistencies in the data--wide variations within individuals on different trials--possibly from unusually large experimental errors or misspecified pharmacokinetic model.
Dell, 1980 et al.	Indomethacin Acemetacin	Not possible to correct for body weight
Dahlqvist, 1984 et al.	Theophylline	Not possible to correct for body weight
Dayer, 1983	Bufuralol toxicity	Parameter too difficult to relate to
Dayer, 1985 et al.	Atenolol, Bopindolol, Metroprolol	Not possible to correct for body weight
Dick, 1982 et al.	Debrisoquin	Urinary excretion data too difficult to relate directly to susceptibility
Fotherby, 1981 et al.	Ethyloestra-diol	Not possible to correct for body weight
Grant, 1983 et al.	Caffeine	Parameter too difficult to relate to toxicity
Green, 1984 et al.	Tobramycin	Too difficult to relate to toxicity
Inaba, 1981 et al.	Debrisoquine	Urinary excretion data too difficult to relate directly to susceptibility.
Levy, 1981	Aspirin	Not possible to correct for body weight

TABLE 3 (cont.)

First Author, Year	Chemical	Reason for Exclusion
McAinsh, 1980 et al.	Atenolol	Not possible to correct for body weight
Midha, 1983 et al.	Fluphenazine	Too few subjects treated in identical fashion
Mitchell, 1984 et al.	S-carboxymethyl -l-cysteine	No obvious relationship to toxicity
Neuvonen, 1983	Chlorpropamide	Not possible to distinguish individual data from individual trials
Oates, 1982 et al.	Phenformin	Urinary excretion data too difficult to relate directly to susceptibility.
Parker, 1984 et al.	Metoprolol, Nadolol, Propranolol	Not possible to correct for body weight
Pfaff, 1983	Dextromethor-phan	Subjects selected to be sure that urinary and plasma drug concentrations were in specific ranges.
Reiter, 1982	Acetaminophen	Urinary excretion data too difficult to relate directly to susceptibility.
Veulemans, 1979	Toluene	Body weight correction not possible. Urinary excretion data not directly relatable to susceptibility to toxicity.
Watson, 1982 et al.	Salt	Body weight correction not possible. Urinary salt excretion rate not directly relatable to susceptibility to toxic action.
Yacobi, 1981 et al.	Digoxin	Body weight correction not possible.

3. METHODS OF ANALYSIS

The major challenge of the data analysis was to quantify the observed variability of pharmacokinetic parameters in ways that are both readily understandable by risk analysts and are as faithful as possible in representing the complexity of the results of the experiments. To do this, the data were summarized in two fundamentally different ways:

(1) As summary statistics that assume different underlying forms for the population distribution -- geometric and arithmetic standard deviations. The use of the geometric standard deviation for risk assessment would presuppose a log-normal form for the underlying population distribution of the parameter studied (that is, that the logarithms of $T_{1/2}$, AUC, are normally distributed); the arithmetic standard deviation would be more appropriate if the underlying population distribution of the parameter were normal.

Under the log-normal calculation model, interindividual variability is represented as the log(geometric standard deviation) -- which is analogous to the representation of variability in the second column of Table 1 (See Introduction). The variability under the arithmetic-normal distribution model is represented as the "coefficient of variation" -- which is simply the arithmetic standard deviation divided by the mean of the parameter under study. (One might generally expect a log-normal model to be appropriate if the factors contributing to interindividual differences were numerous and interacted with each other multiplicatively. By contrast an arithmetic-normal distribution would be expected if different factors contributing to interindividual variability were numerous and made additive contributions. On the other hand a bi- or multimodal distribution might be produced if there were only a few major factors or states that were responsible for much of the interindividual variability in susceptibility.)

(2) A method that makes no assumptions about the underlying form of the distribution. This is based on the empirical cumulative distribution function of Wilk and Gnanadesikian (1968). The values are placed in increasing order, X_1, X_2, ..., X_i and assigned a "percentage score" equal to $(i - 0.5)/N$ where N is the total number of individuals studied. These "percentage scores" represent estimates of the fraction of an infinite-sized population of values from the same distribution that would be below each X_i.*

We then interpolated between adjacent X_i's to estimate the values of the distribution at a set of standard "percentage scores" -- the 70th, 30th, and (where the sample size was at least 10) the 95th and 5th. The interindividual variability of the distribution could then be represented by a pair of ratios symmetric about the median. The "70/30 ratio" is simply the ratio of the interpolated values of the distribution at the 70th and 30th percentage scores, and similarly the "95/05 ratio" is the ratio of the interpolated values at the 95th and 5th percentage score points. For distributions that are truly log-normal, these two ratios represent approximately 1.05 and 3.29 standard deviations, respectively.

A final caveat that must be attached to both of these procedures is that they basically summarize the raw distibutions of values found in the data. Part of the variability in such distributions is produced by experimental measurement error, rather than true variability of the parameters studied between subjects. An ideal procedure to determine true variability for purposes of modeling the true distribution of responsiveness in a diverse population would be to assess and subtract variation due to experimental measurement error.

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*These "percentage scores" are <u>not</u> the same as "percentiles" calculated by usual procedures. Generally in calculating percentiles, the highest <u>observed</u> value is considered to be the 100th percentile. However, in a limited sample of observations, one cannot expect that the highest possible value of the parameter being measured is included. This results in a bias related to sample size near the tails of the distribution for relatively small sample sizes. Generally, one should expect that if a series of samples of size N were drawn, approximately half should contain a value larger than the highest value in the initial sample of N. Therefore, as specified by the Wilk and Gnanadeskikian formula, it is reasonable to assign the highest of N values a percentage score of (N - 0.5)/N (i.e. 0.95 for the highest value in a sample of 10).

4. DATA BASE STRUCTURE AND TERMINOLOGY

Data and bibliographic information were entered into a data base on MIT's IBM mainframe computer using the FOCUS data base management system (Information Builders, 1983). The bibliographic portion of the data base (e.g. title, author, journal) was drawn from the MIT's "Bibliographic Management System" (Priest, 1982).

Figure 1 (01) and (02) shows the basic structure of the data base, and Table 4 shows the "master file" that formally defines the various fields. The fields are grouped in a series of "segments" that can have a logical hierarchical relationship. For example, all information arising from each paper is grouped under a 12-character master paper identifier (IDENTITY) contained in the master "IDS" segment. Some individual papers contained more than one "experiment" (by an "experiment" we mean a single series of administrations of a particular compound to a single set of subjects). Therefore, as can be seen from Figure 1 (02), an "Exper" segment contains data that characterizes each experiment (EXPNO), including the chemical involved (CHEMICAL), the mode of administration (MODE ADMIN), the dosage (DOSAGE), the population studied (POP), and any peculiarities of the experimental situation or data analysis (COMMENT). The different experiments within each paper are each assigned an individual number (EXPNO). Within a particular experment, more than one parameter may have been measured. Therefore the data base provides for the possibility of multiple "Dataset" segments within each "Exper" segment. Each data set is characterized as to the parameter type (PAR -- e.g. $T_{1/2}$, Cmax), exactly which figure or table in the paper provided the data (SOURCE), the units used for expressing the parameter (UNITS), and various summary statistics calculated from the data:

SECTION 01

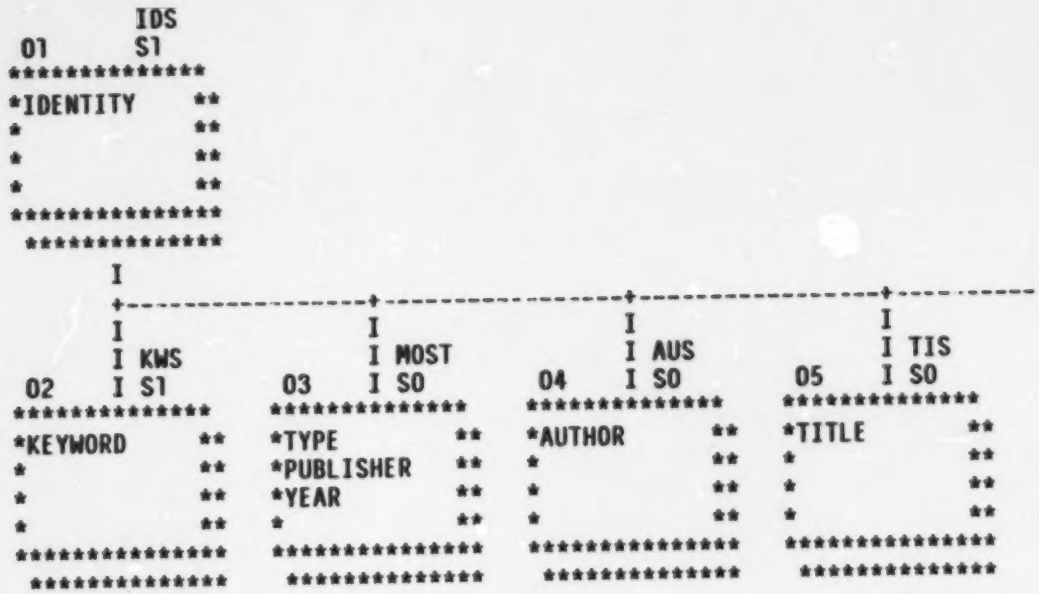

FIGURE 1

Data Base Structure

SECTION 02

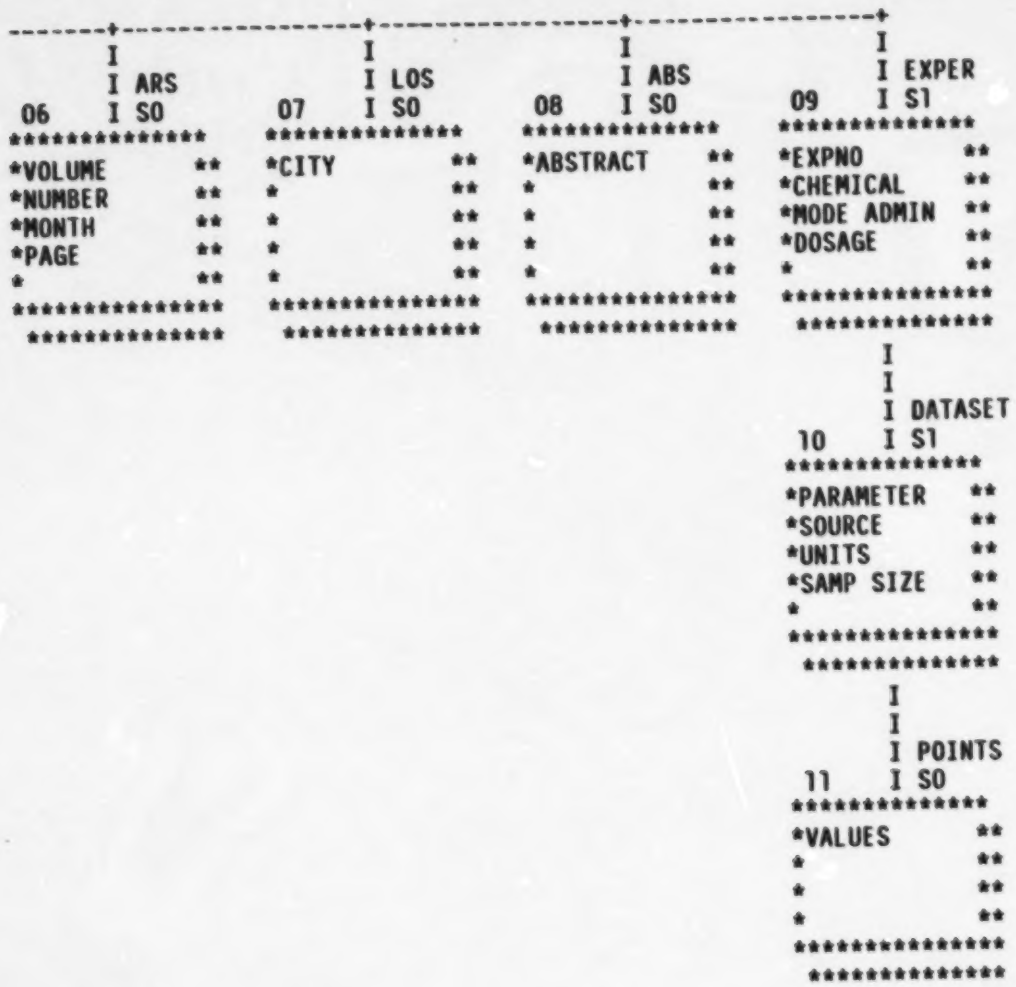
06 I ARS I SO
*VOLUME **
*NUMBER **
*MONTH **
*PAGE **
* **
07 I LOS I SO
*CITY **
* **
* **
* **
* **
08 I ABS I SO
*ABSTRACT **
* **
* **
* **
* **
09 I EXPER I S1
*EXPNO **
*CHEMICAL **
*MODE ADMIN **
*DOSAGE **
* **
10 I DATASET I S1
*PARAMETER **
*SOURCE **
*UNITS **
*SAMP SIZE **
* **
11 I POINTS I SO
*VALUES **
* **
* **
* **

TABLE 4
Data Base "Master File" (Dictionary)

```
FILENAME=I, SUFFIX=FOC,$
SEGMENT=IDS, SEGTYPE=S1,$
  FIELD=IDENTITY,ALIAS=id,USAGE=A12,$
SEGMENT=KWS,SEGTYPE=S1,PARENT=IDS,$
  FIELD=KEYWORD,ALIAS=ke,USAGE=A27,$
SEGMENT=MOST,SEGTYPE=S0,PARENT=IDS,$
  FIELD=TYPE,ALIAS=ty,USAGE=A1,$
  FIELD=PUBLISHER,ALIAS=pu,USAGE=A80,$
  FIELD=YEAR,ALIAS=ye,USAGE=I4,$
SEGMENT=AUS,SEGTYPE=S0,PARENT=IDS,$
  FIELD=AUTHOR,ALIAS=au,USAGE=A27,$
SEGMENT=TIS,SEGTYPE=S0,PARENT=IDS,$
  FIELD=TITLE,ALIAS=ti,USAGE=A76,$
SEGMENT=ARS,SEGTYPE=S0,PARENT=IDS,$
  FIELD=VOLUME,ALIAS=vo,USAGE=I6,$
  FIELD=NUMBER,ALIAS=nu,USAGE=I6,$
  FIELD=MONTH,ALIAS=mo,USAGE=A12,$
  FIELD=PAGE,ALIAS=pa,USAGE=A10,$
SEGMENT=LOS,SEGTYPE=S0,PARENT=IDS,$
  FIELD=CITY,ALIAS=ci,USAGE=A20,$
SEGMENT=ABS,SEGTYPE=S0,PARENT=IDS,$
  FIELD=ABSTRACT,ALIAS=ab,USAGE=A76,$
SEGMENT=EXPER,SEGTYPE=S1,PARENT=IDS,$
  FIELD=EXPNO,ALIAS=NO,USAGE=I2,$
  FIELD=CHEMICAL,ALIAS=CHEM,USAGE=A20,$
  FIELD=MODE_ADMIN,ALIAS=MAD,USAGE=A20,$
  FIELD=DOSAGE,ALIAS=DOS,USAGE=A40,$
  FIELD=POPULATION,ALIAS=POP,USAGE=A60,$
  FIELD=COMMENT,ALIAS=COM,USAGE=A76,$
SEGMENT=DATASET,SEGTYPE=S1,PARENT=EXPER,$
  FIELD=PARAMETER,ALIAS=PAR,USAGE=A10,$
  FIELD=SOURCE,ALIAS=SO,USAGE=A20,$
  FIELD=UNITS,ALIAS=UN,USAGE=A40,$
  FIELD=SAMP_SIZE,ALIAS=N,USAGE=I4,$
  FIELD=MEAN,ALIAS=MN,USAGE=D10.4,$
  FIELD=COEF_VAR,ALIAS=CV,USAGE=D5.3,$
  FIELD=SKEWNESS,ALIAS=SK,USAGE=D8.4,$
  FIELD=KURTOSIS,ALIAS=KUR,USAGE=D8.4,$
  FIELD=GEOM_MEAN,ALIAS=GMN,USAGE=D8.4,$
  FIELD=GEOM_SD,ALIAS=GSD,USAGE=D7.3,$
  FIELD=GSKEW,ALIAS=GSKEW,USAGE=D8.4,$
  FIELD=GKURT,ALIAS=GKURT,USAGE=D8.4,$
  FIELD=70_30RATIO,ALIAS=R1,USAGE=D7.3,$
  FIELD=95_05RATIO,ALIAS=R2,USAGE=D7.3,$
SEGMENT=POINTS,SEGTYPE=S0,PARENT=DATASET,$
  FIELD=VALUES,ALIAS=VAL,USAGE=D10.4,$
```

SAMP SIZE -- The number of individuals on which measurements were made.

MEAN -- The arithmetic average of the measurements.

COEF VAR -- The coefficient of variation (the arithmentic standard deviation divided by the mean).

SKEWNESS -- The third moment of the distribution, equal to the sum of $[(X_1 - \text{mean}(X))/S]^3/N$ where S is the standard deviation and mean(X) is the average of all the individual values, X_1. This is a measure of the symmetry or asymmetry of the distribution. For an arithmetic-normal distribution, the skewness should be near 0. A positive skewness indicates that there are relatively more high values of the distribution than would be expected if the distribution were perfectly normally distributed.

KURTOSIS -- The fourth moment of the distribution, equal to the sum of $([(X_1 - \text{mean}(X))/S]^4/N) - 3$. This is a measure of the flatness or peakedness of the distribution. For a normal distribution the Kurtosis is 0. A negative value for the kurtosis indicates that the distribution is flatter than might be expected for a normal distribution, as might occur if the distribution had some tendency to be multi-modal, for example.

GEOM MEAN -- The mean of the logarithms$_{10}$ of the measurements. Similarly, GEOM_SD, GSKEW, and GKURT are the standard deviation, skewness, and kurtosis of the log$_{10}$ values.

70 30RATIO and 95 05RATIO -- As discussed in the previous section, these are the ratios of the expected values of the distribution at the 70 and 30 percentage scores, and the similar ratio of the values of the distribution at the 95 and 5 percentage scores.

Finally, for each parameter there are a number of individual measurements. The individual VALUES are stored in a "Points" segment. Appendix A is a printout of the information in the data base that is stored at the "Dataset" level and above. In all, the data base includes 1560 individual values in 101 data sets from 75 separate experiments covering 49 different chemicals. The "IDENTITY" number in the leftmost column of Appendix A can be used to identify the reference cited in the bibliography with following decoding information:

- The second, third, fourth, and fifth letters of the IDENTITY string are the first four letters of the first author's last name.
- The sixth letter of the string is the first letter of the first author's first name.

- The seventh and eighth characters of the string give the year of publication.
- Finally, the last four letters in the string are the first letters in the first four major words in the title of the paper.
- A printout of the data is included in the Appendix.

5. RESULTS

5.1. Forms of the Distributions -- Inferences from Skewness and Kurtosis Statistics

Before exploring the overall amounts of variability indicated in the data, it is helpful to examine the skewness and kurtosis statistics to see what they suggest about the underlying forms of the distributions. Seventy-two of the 101 data sets have a positive value for skewness. This is significantly more than the 50% that could be expected by chance (Chi^2 = 18.3, P <0.001) if the underlying distributions were all arithmetic-normal. The apparent asymmetry is in the direction that would be expected if the distributions were more nearly log-normal. When the skewness of the distributions of the logarithms of the values is examined (GSKEW), one still finds a slight apparent excess of positive skewness values (57/101) but this difference is not statistically significant (chi^2 = 1.67, P greater than 0.1).

The apparent agreement with the expectations one might have under a log-normal theory is reduced when one analyzes the kurtosis of the distributions of the logarithms of the values. Fully 93/101 of the GKURT values are negative, indicating a somewhat flatter middle section and heavier "tails" than would be expected under a pure unimodal log-normal theory. One possible explanation for this finding is that there may often be some degree of bi- or multimodality in the data sets. This should be explored in future work.

Because the skewness data indicate that the log-normal distribution may often be closer to the actual form of the data than the normal distribution, the summary tables in the following section will focus on the $\log_{10}$ geometric standard deviation statistics. In any case the log-normal

geometric standard deviation is the measure that most closely parallels the summarization of animal data by Weil, (1972) and the presumption of the "Vulnerability Model" log probit risk equations (Eisenberg and Lynch, 1975). However, because of the apparent departure of the kurtosis statistics from expectations under a pure log-normal theory, we will use the non-distributional 70/30 and 95/05 ratios to characterize the data as well as the log-normal geometric standard deviations in some of the summary analysis.

5.2. Apparent Variability of Pharmacokinetic Parameters

Tables 5 through 8 show the results for individual data sets, ordered from the highest to the lowest geometric standard deviations. Table 5 shows the most frequent parameter measured -- 61 data sets for elimination half lives. Table 6 shows data for AUC and steady state concentration measurements, and Table 7 gives data on the maximum concentrations observed in blood after administration (or, on some cases, the bood concentration at a defined time point such as 12 hours). Some miscellaneous data sets are shown in Table 8 (the latter parameters generally were the reciprocals of metabolism or kidney clearance rates, which could not be transformed into whole-body elimination $T_{1/2}$'s because of limitations in the information contained in the papers. Table 9 gives some summary statistics for the geometric standard deviations for all 101 data sets.

The $T_{1/2}$ and Cmax data (Tables 5 and 7) both have median values of Log_{10} geometric standard deviations somewhat over 0.11 -- not very different, in other words, from the <u>total</u> geometric standard deviation of susceptibility of 0.0934 - 0.114 assumed for chlorine and ammonia in the Coast Guard's "Vulnerability Model" (Eisenberg and Lynch 1975). There seems to be some tendency toward greater amounts of interindividual variability in data sets where AUC or steady state concentrations were the measured

TABLE 5

Interindividual Variability of Elimination Half-Lives ($T_{1/2}$)

Duplicate Determinations for Individual Chemicals Not Combined

Chemical	Sample Size	Log_{10} Geom SD	70/30 Ratio	95/05 Ratio
Sulfadimidine	152	0.261	2.357	6.736
Dicumarol	14	0.259	1.508	6.910
Sulfamethazine	5	0.258	1.031	-
Mefruside	8	0.243	2.441	-
Cimetidine	10	0.226	1.769	5.222
Clobazam	12	0.210	1.609	3.785
Tolbutamide	50	0.189	1.414	3.889
Phenylbutazone	14	0.175	1.292	4.818
Antipyrine	6	0.170	1.393	-
Nortriptyline	35	0.168	1.400	3.243
Antipyrine	8	0.167	1.298	-
Morphine	7	0.167	1.761	-
Theophylline	30	0.151	1.414	3.348
Nicotine	14	0.149	1.391	2.363
Trimazosin	6	0.147	1.740	-
Viloxazine	16	0.143	1.450	3.878
Sulfinpyrazone	5	0.142	1.412	-
Norepinephrine	5	0.139	1.718	-
Gentamicin	10	0.139	1.411	2.916
Quinidine	12	0.136	1.291	2.599
Theophylline	6	0.133	1.332	-
Hexobarbital	29	0.128	1.363	2.316
Terbutaline	6	0.128	1.556	-
Propranolol	27	0.126	1.200	2.826
Propylthiouracil	10	0.121	1.350	2.329
Phenylbutazone	8	0.120	1.242	-
Theophylline	15	0.120	1.429	2.437
Trimazosin	6	0.120	1.557	-
Sulfamethazine	5	0.120	1.306	-
Lithium	24	0.118	1.477	2.562
Nortriptyline	6	0.116	1.491	-
Diltiazem	12	0.110	1.122	2.490
Antipyrine	14	0.110	1.235	2.168
Triazolam	8	0.106	1.342	-
Cimetidine	20	0.106	1.316	2.226
Brotizolam	8	0.105	1.334	-
Antipyrine	8	0.105	1.218	-

TABLE 5 (cont.)

Chemical	Sample Size	Log_{10} Geom SD	70/30 Ratio	95/05 Ratio
Nifedipine	6	0.097	1.168	-
Trichloroethylene	5	0.091	1.093	-
Nifedipine	9	0.091	1.386	-
Theophylline	91	0.088	1.229	1.745
Metoclopramide	6	0.087	1.247	-
Trimethoprim	6	0.086	1.085	-
Bromazepam	10	0.085	1.115	1.843
Cimetidine	10	0.083	1.307	1.666
Metoprolol	8	0.083	1.173	-
Dixyrazine	8	0.083	1.265	-
Acetaminophen	8	0.081	1.123	-
Acetaminophen	12	0.080	1.311	1.695
Amitriptyline	6	0.080	1.244	-
Phenylpropanolamine	7	0.077	1.158	-
Bromazepam	10	0.075	1.158	1.868
Antipyrine	20	0.073	1.215	1.758
Metoclopramide	6	0.071	1.062	-
Mexiletine	5	0.066	1.071	-
Timolol	5	0.062	1.182	-
Ethosuximide	6	0.061	1.093	-
Amikacin	10	0.060	1.162	1.533
Phenacetin	9	0.058	1.181	-
Prifinium bromide	6	0.054	1.161	-
Nitrazepam	6	0.036	1.062	-

Geometric Mean, 61 Data Sets	0.112
Geometric Mean +/- 1 Standard Error	0.106-0.118
Geometric Mean +/- 2 Standard Dev.	0.048-0.260

TABLE 6

Interindividual Variability of "Area Under the Concentration/Time Curve" (AUC) and "Steady State Blood Concentration" (Css)*

Duplicate Determinations for Individual Chemicals Not Combined

Chemical	Sample Size	Log_{10} Geom SD	70/30 Ratio	95/05 Ratio
Dixyrazine	8	0.413	2.819	-
Dixyrazine	8	0.374	2.668	-
Triazolam	8	0.306	1.964	-
Timolol	5	0.278	2.889	-
Sulfamethazine	5	0.231	1.874	-
Viloxazine	16	0.211	1.869	4.797
Metoclopramide	6	0.198	1.928	-
Sulfamethazine	5	0.186	1.245	-
Cimetidine	20	0.147	1.587	2.779
Bromazepam	10	0.146	1.439	2.785
Metoclopramide	6	0.144	1.531	-
Bromazepam	10	0.120	1.349	2.404
Brotizolam	8	0.110	1.287	-
Phenylpropanolamine	8	0.109	1.410	-
Prifinium bromide	6	0.109	1.498	-
Trimethoprim	6	0.104	1.326	-
Aspirin	10	0.103	1.303	2.188
Aspirin	8	0.088	1.216	-
Mexiletine	5	0.070	1.254	-
Valproic Acid	10	0.056	1.162	1.453
Geometric Mean, 20 Data Sets		0.152		
Geometric Mean +/- 1 Standard Error		0.134-0.171		
Geometric Mean +/- 2 Standard Dev.		0.051-0.451		

*All data are corrected for the mg/kg dose given to different individuals.

TABLE 7

Interindividual Variability of Maximum Blood Concentrations C_{max}*

Duplicate Determinations for Individual Chemicals Not Combined

Chemical	Sample Size	Log_{10} Geom SD	70/30 Ratio	95/05 Ratio
Dixyrazine	8	0.406	3.019	-
Dixyrazine	8	0.400	4.281	-
Timolol	5	0.239	2.301	-
Viloxazine	16	0.179	1.681	3.700
Nifedipine	6	0.143	1.257	-
Bromazepam	10	0.136	1.490	2.483
Prifinium bromide	6	0.115	1.400	-
Phenylpropanolamine	8	0.113	1.432	-
Sulfamethazine	5	0.112	1.207	-
Sulfamethazine	5	0.088	1.262	-
Bromazepam	10	0.080	1.175	1.830
Trimethoprim	8	0.077	1.131	-
Metoclopramide	6	0.070	1.254	-
Nifedipine	6	0.062	1.140	-
Valproic Acid	10	0.045	1.097	1.405
Theophylline	7	0.041	1.126	-
Geometric Mean, 16 Data Sets		0.114		
Geometric Mean +/- 1 Standard Error		0.096-0.135		
Geometric Mean +/- 2 Standard Dev.		0.029-0.443		

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*Also included in this data are some sets of measurements of blood concentrations at a particular time point--i.e., 12 hours after administration.
All data are corrected for the mg/kg dose given to different individuals.

TABLE 8

Interindividual Variability of Other Parameters
(Generally 1/Metabolism Rates or 1/Renal Clearance Rates)

Duplicate Determinations for Individual Chemicals Not Combined

Chemical	Sample Size	Log_{10} Geom SD	70/30 Ratio	95/05 Ratio
N-Formimidoyl Thienamycin	11	0.277	2.191	5.475
Antipyrine	310	0.154	1.500	3.125
Ethanol	20	0.095	1.304	1.931
Insulin	21	0.070	1.222	1.653
Geometric Mean, 4 Data Sets		0.130		
Geometric Mean +/- 1 Standard Error		0.096-0.175		
Geometric Mean +/- 2 Standard Dev.		0.039-0.432		

TABLE 9

Summary Statistics for Log_{10} Geometric Standard Deviations
For all 101 Datasets

Duplicate Determinations for Individual Chemicals Not Combined

Geometric Mean, 101 Data Sets	0.120
Geometric Mean +/- 1 Standard Error	0.114-0.126
Geometric Mean +/- 2 Standard Dev.	0.043-0.331

parameters (Table 7). In this case the median $\log_{10}$ geometric standard deviation is about 0.145 and three of the 20 data sets were over 0.3 (compared with none of 61 data sets over 0.3 in the case of $T_{1/2}$). For both AUC and Cmax data sets, the two largest geometric standard deviations were observed for dixyrazine. Dixyrazine is evidently a highly lipophilic compound for which there is substantial interindividual variability in absorption and/or "first pass" metabolism in the liver (Liedholm et al., 1985). As can be seen in Table 5, the interindividual variability in dixyrazine's elimination half-life is not remarkable.

In terms of the 70/30 and 95/05 ratios, median values for all parameters are in the range of 1.3 and 2.5 respectively. This is approximately what would be expected under a log-normal theory for the distribution of the underlying parameters. The median value of the 101 $\log_{10}$ geometric standard deviations is 0.116. If the 70/30 and 95/05 ratios correspond to 1.05 and 3.29 standard deviations, then under a log-normal theory one should expect the median 70/30 ratio to be $10^{1.05*.116} = 1.32$. Similarly, under a log-normal theory one should expect the median 95/05 ratio to be $10^{3.29*0.116} = 2.41$. We can do the same comparison at another point in the distribution of our different measures of interindividual variability. The 90th percentiles of the distributions of $\log_{10}$ geometric standard deviation, 70/30 ratio, and 95/05 ratio are approximately 0.25, 1.95 and 5.0 respectively. Under a log-normal theory one would expect the 90th percentile of the 70/30 ratio to be $10^{1.05*0.25} = 1.83$ and one would similarly expect the 90th percentile of the 95/05 ratio to be $10^{3.29*0.25} = 6.65$. The second comparison of 95/05 ratios may be somewhat off in part because the five dixyrazine data sets all were based on less than 10 individuals, and therefore did not contribute to the set of 95/05 ratios. In all,

expectations under a log-normal theory do not appear to be markedly different from the observations of actual 70/30 and 95/05 ratios.

Table 10 shows the $\log_{10}$ geometric standard deviation results after combining duplicate determinations for the same parameter in different trials for the same chemical*. Table 11 gives summary statistics for the total of all 75 chemical/parameter combinations.

As observed previously in the results at the level of individual data sets, there is some suggestion that the AUC/Css** measurements show more interindividual variability than the $T_{1/2}$ measurements. This might be expected from theory, as the AUC data include some contribution from variability in absorption in addition to variability in elimination. The difference between the geometric means at the bottom of Table 10 is statistically significant at P less than 0.05 (t = 1.89 with 57 degrees of freedom). There is also some indication in the data that particularly large amounts of interindividual variability are more commonly observed for both AUC and peak concentration measurements than for measurments of elimination half life. The ranges encompassing 2 standard deviations from the mean is 0.045 - 0.269 for $T_{1/2}$, compared with 0.048 - 0.439 and 0.03 - 0.399 for AUC and peak concentration data respectively. In other words, if the

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*This combination was done using an approximate procedure based on a simple calculation of within-group variances. Within-group variances for each trial were computed by squaring the $\log_{10}$ geometric standard deviations listed in Table 5-8, and the results were multiplied by the numbers of individuals studied in each trial minus 1 to reconstruct the sum of the squared deviations from the $\log_{10}$ geometric mean. An approximate aggregate $\log_{10}$ geometric standard deviation was then computed as the square root of the sum of all the squared deviations from each data set divided by (N-K), where N was the total number of individuals and K was the total number of data sets. This procedure implicitly treats all between-group differences as due to systematic error and hence may somewhat underestimate the true interindividual variability.

**Css: Steady State concentration.

TABLE 10

Log_{10} Geometric Standard Deviations for Different Parameters

After Combining Duplicate Determinations for Individual Chemicals

$T_{1/2}$		AUC*		Peak Concentration**	
Sulfadimidine	0.261	Dixyrazine	0.403	Dixyrazine	0.403
Dicumarol	0.259	Triazolam	0.306		
		Timolol	0.278		
Mefruside	0.243	Viloxazine	0.211	Timolol	0.239
Clobazam	0.210	Sulfamethazine	0.210	Viloxazine	0.179
Sulfamethazine	0.201	Metoclopramide	0.173		
Tolbutamide	0.189				
Morphine	0.167				
Nortiptyline	0.162	Cimetidine	0.147		
Phenylbutazone	0.158	Bromazepam	0.134		
Nicotine	0.149				
Viloxazine	0.143				
Sulfinpyrazone	0.142				
Cimetidine	0.141				
Gentamicin	0.139				
Norepinephrine	0.139				
Quinidine	0.136				
Trimazosin	0.134				
Hexobarbital	0.128				
Terbutaline	0.128				
Propranolol	0.126				
Propylthiouracil	0.121	Brotizolam	0.110	Prifinium bromide	0.115L
ithium	0.118	Phenylpropanol-amine	0.109	Phenylpropanol-amine	0.113
Antipyrine	0.115	Prifinium bromide	0.109	Bromazepam	0.112
Diltiazem	0.110	Trimethoprim	0.104	Nifedipine	0.110
Theophylline	0.109			Sulfamethazine	0.101
Triazolam	0.106				
Brotizolam	0.105				
Nifedipine	0.093	Aspirin	0.097		
Trichloro-ethylene	0.091				
Trimethoprim	0.086				

TABLE 10 (Cont.)

$T_{1/2}$		AUC*		Peak Concentration**	
Dixyrazine	0.083	Mexiletine	0.070	Trimethoprim	0.077
Metoprolol	0.083			Metoclopramide	0.070
Acetaminophen	0.080				
Amitriptyline	0.080				
Bromazepam	0.080				
Metoclopramide	0.079				
Phenylpropanol-amine	0.077				
Mexiletine	0.066				
Timolol	0.062	Valproic acid	0.056	Valproic acid	0.045
Ethosuximide	0.061			Theophylline	0.041
Amikacin	0.060				
Phenacetin	0.058				
Prifinium bromide	0.054				
Nitrazepam	0.036				
Number of Chemicals	44		15		12
Geom. Mean	0.111		0.145		0.109
+/- 1 S.E.M.	0.103-0.118		0.126-0.168		0.090-0.131
+/- 2 Std. Dev.	0.045-0.269		0.048-0.439		0.030-0.399

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*Or steady-state concentration in blood.
**Or concentration in blood at a defined time after dosing, i.e., 12 hours.

TABLE 11

Summary Statistics for Log_{10} Geometric Standard Deviations
For Measurements of Individual Parameters for Specific Chemicals

Results After Combination of Duplicate Determinations of the Same Parmeter for Individual Chemicals

Geometric Mean, 75 Chemical/Parameter Sets	0.118
Geometric Mean +/- 1 Standard Error	0.111-0.125
Geometric Mean +/- 2 Standard Dev.	0.042-0.328

$\log_{10}$ geometric standard deviations are themselves log normally distributed, we should expect that about 2% of the observations of $\log_{10}$ geometric standard deviations of T1/2 for individual chemicals will be above 0.27, whereas for AUC and peak concentration data, 2% of the chemicals may be as high as 0.4. This result, however, is heavily influenced by the observations for one chemical -- dixyrazine.

Using these same data, Table 12 compares the apparent variability for different pharmacokinetic parameters in humans with the overall distributions of susceptibility for acute lethality inferred from the animal data by Weil (1972). The result is that the interindividual variability in specific pharmacodynamic parameters for the 49 agents studied in groups of normal healthy adult humans does not depart markedly from the Weil (1972) distribution of <u>total</u> variability in susceptibility to acute lethal effects of chemicals in groups of rats. Where Weil found that about 14% of the rat data sets had $\log_{10}$ geometric standard deviations of over 0.25, the proportion of chemicals showing this degree of interindividual variability in specific pharmacokinetic parameters was approximately 5% for elimination half lives (2/44), 20% for AUC measurements (3/15), 8% for peak blood concentrations (1/12). One of the four observations in a miscellaneous set of "other" parameters (Table 8) was also above this level of indicated interindividual variability.

Table 12

Comparison of Variability For Human Susceptibility Components with the Apparent Distribution of Log-Probit Dose Response Slopes Observerved in Oral LD_{50} Determinations in Rats

After Combination of Duplicate Determinations for Individual Chemicals

Log Std. Dev.	Cumulative % of Observations in Animals (Weill Data)	Observation In Humans							
		$T_{1/2}$ No.	$T_{1/2}$ Cum %	AUC or Css No.	AUC or Css Cum %	C_{max} No.	C_{max} Cum %	All* Parameters No.	All* Parameters Cum %
0.5-0.71	1.4								
0.25-0.5	13.7	2	5	3	20	1	8	7	9
0.1667-0.25	32.0	5	16	3	40	2	25	10	23
0.125-0.1667	51.8	13	45	2	53			16	44
0.1-0.125	66.3	7	61	4	80	5	67	16	65
0.085-0.1	78.0	3	68	1	87			5	72
0.0625-0.085	88.8	8	86	1	93	2	83	12	88
0.045-0.0625	95.7	5	98	1	100	2	100	8	99
0.0333-0.045	98.4	1	100					1	100
0.0154-0.0333	100	---		--		--		--	
	Total	44		15		12		75*	

*Note: The numbers of observations in the final column include the four "other" parameters (see Table 8) that are not represented in the first three columns.

6. DISCUSSION

Particularly with respect to the comparisons made in Table 12, it should be reemphasized that the parameters studied in humans are only components of overall susceptibility to toxic agents, and do not include contributions from variability in exposure- and response-determining parameters. The data also include no contribution to variability from diseased or other special sub- populations -- and it is these types of sensitive subpopulations that have often been of major concern for standard setting under environmental laws such as the Clean Air Act. Also, it is not entirely clear how the results of this analysis of short-term pharmacokinetic observations relate to chronic toxicity, although elimination half lives certainly represent at least one parameter that seems likely to generally influence susceptibility to toxic effects from long term exposures. Therefore the results of this very limited comparison only provide direct evidence that the degree of interindividual variation among normal healthy humans is not less than that expected from the experimental animal data. The effect of other factors contributing to the total population variability in susceptibility to toxicants is not measured and could be greater.

The numbers of chemicals and human parameters summarized to date are clearly quite small, both relative to the available human literature and to the animal data set compiled by Weil (1972). Based on the limited survey of the literature undertaken, it seems likely that the overall data base assembled here could be expanded 3-fold to 6-fold with a relatively straightforward extension of the present work. Future work should also clearly include studies of "exposure" and "response" parameters, and studies in patient and various "special" subpopulations likely to depart significantly from average susceptibility among normal healthy adults. It is also

important to document whether instances of relatively greater apparent variability are associated with different structural categories of chemical agents, different modes of administration, age-restricted vs. not age-restricted population samples, and other study characteristics. Finally, the lessons from these different analyses should be integrated into predictive models of human interindividual variability as an aid for quantitative human risk assessment for toxic chemical exposures.

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APPENDIX A -- DETAILED CONTENTS OF THE DATA BASE ON HUMAN VARIABILITY

(See Section 4 of the text for definitions of terms.)

IDENTITY	EXPND												
IAHLMJ82PTGI	1	CHEMICAL	Trimethoprim	PARAMETER	C(12 hr)	SAMP_SIZE	8	COEF_VAR	.171	GEOM_SD	.077		
		MEAN	.6840	GEOM_MEAN	-.1710	70_30RATIO	1.131	95_05RATIO	.000				
		SKEWNESS	-.0680	GSKEW	-.4650	KURTOSIS	-.6810	GKURT	-.5460				
		DOSAGE	300 mg tablet				MODE_ADMIN	0					
		POPULATION	8 healthy volunteers, 17-66 yrs, 2 male				SOURCE	Table I, p. 144					
		UNITS	(ug/ml)/(mg/kg dose)										
		COMMENT											
IALLEJ83SSSP	1	CHEMICAL	Aspirin	PARAMETER	Css	SAMP_SIZE	10	COEF_VAR	.226	GEOM_SD	.103		
		MEAN	.3180	GEOM_MEAN	-.5090	70_30RATIO	1.303	95_05RATIO	2.188				
		SKEWNESS	-.0090	GSKEW	-.3420	KURTOSIS	-1.1820	GKURT	-1.1610				
		DOSAGE	3.9 g in 3 pre-meal doses				MODE_ADMIN	0					
		POPULATION	12 healthy ss, less 2 dropouts				SOURCE	Table I, p. 65					
		UNITS	(mg/dl)/(mg/kg dose)										
		COMMENT	Mean steady state plasma salicylate (days 3-4) for 4 different preps										
IALTAA83ARDI	1	CHEMICAL	Viloxazine	PARAMETER	AUC	SAMP_SIZE	16	COEF_VAR	.467	GEOM_SD	.211		
		MEAN	18.1730	GEOM_MEAN	1.2130	70_30RATIO	1.869	95_05RATIO	4.797				
		SKEWNESS	.6050	GSKEW	-.1640	KURTOSIS	-.3580	GKURT	-1.1600				
		DOSAGE	200 mg				MODE_ADMIN	0					
		POPULATION	1st 8 subjects are 25-46; 2nd 8 are 62-90 years				SOURCE	p. 282, table 1					
		UNITS	ug*hr/ml/m										
		COMMENT											
		CHEMICAL	Viloxazine	PARAMETER	Cmax	SAMP_SIZE	16	COEF_VAR	.418	GEOM_SD	.179		
		MEAN	2.2550	GEOM_MEAN	.3190	70_30RATIO	1.681	95_05RATIO	3.700				
		SKEWNESS	.7640	GSKEW	.0530	KURTOSIS	-.0910	GKURT	-1.0900				
		DOSAGE	200 mg				MODE_ADMIN	0					
		POPULATION	1st 8 subjects are 25-46; 2nd 8 are 62-90 years				SOURCE	p. 282, table 1					
		UNITS	ug/l/mg/kg										
		COMMENT											
		CHEMICAL	Viloxazine	PARAMETER	T1/2	SAMP_SIZE	16	COEF_VAR	.318	GEOM_SD	.143		
		MEAN	10.2980	GEOM_MEAN	.9910	70_30RATIO	1.450	95_05RATIO	3.878				
		SKEWNESS	.3490	GSKEW	-.2620	KURTOSIS	-.7950	GKURT	-.7260				
		DOSAGE	200 mg				MODE_ADMIN	0					
		POPULATION	1st 8 subjects are 25-46; 2nd 8 are 62-90 years				SOURCE	p. 282, table 1					
		UNITS	hr										
		COMMENT											
IBAUEL84DVIV	1	CHEMICAL	Valproic Acid	PARAMETER	Cmax	SAMP_SIZE	10	COEF_VAR	.108	GEOM_SD	.045		
		MEAN	7.9190	GEOM_MEAN	.8960	70_30RATIO	1.097	95_05RATIO	1.405				
		SKEWNESS	.6240	GSKEW	.4890	KURTOSIS	-.9310	GKURT	-1.0610				
		DOSAGE	250 mg every 12 hours for 4 days				MODE_ADMIN	0					
		POPULATION	7 healthy men and 3 healthy women				SOURCE	Table II, Page 506					
		UNITS	(mg/liter serum)/(mg/kg dosage)										
		COMMENT	All data are averages of morning and evening readings.										
		CHEMICAL	Valproic Acid	PARAMETER	Css	SAMP_SIZE	10	COEF_VAR	.132	GEOM_SD	.056		
		MEAN	6.2270	GEOM_MEAN	.7910	70_30RATIO	1.162	95_05RATIO	1.453				
		SKEWNESS	.4950	GSKEW	.3770	KURTOSIS	-1.3320	GKURT	-1.4170				
		DOSAGE	250 mg every 12 hours for 4 days				MODE_ADMIN	0					
		POPULATION	7 healthy men and 3 healthy women				SOURCE	Table II, Page 506					
		UNITS	(mg/liter serum)/(mg/kg dosage)										

IDENTITY	EXPNO											
		COMMENT All data are averages of morning and evening readings.										
IBENON82IVIM	1	CHEMICAL Nicotine	PARAMETER T1/2		SAMP_SIZE	14	COEF_VAR	.371	GEOM_SD	.149		
		MEAN 119.3570	GEOM_MEAN 2.0520	70_30RATIO	1.391	95_05RATIO	2.363					
		SKEWNESS 1.1640	GSKEW .3130	KURTOSIS	1.1550	GKURT	-.5220					
		DOSAGE 1-2 mg/kg-min			MODE_ADMIN IV							
		POPULATION 14 healthy men, 14-34 years			SOURCE							
		UNITS min										
		COMMENT										
IBREID83VIHD	1	CHEMICAL Nortriptyline	PARAMETER T1/2		SAMP_SIZE	35	COEF_VAR	.446	GEOM_SD	.168		
		MEAN 32.7990	GEOM_MEAN 1.4820	70_30RATIO	1.400	95_05RATIO	3.243					
		SKEWNESS 1.6550	GSKEW .5740	KURTOSIS	3.1970	GKURT	-.0950					
		DOSAGE Not stated			MODE_ADMIN Not stated							
		POPULATION 35 healthy subjects			SOURCE Fig. 3, p. 401							
		UNITS hr										
		COMMENT Data taken from a histogram. Values represent midpoints of ranges.										
	2	CHEMICAL Tolbutamide	PARAMETER T1/2		SAMP_SIZE	50	COEF_VAR	.574	GEOM_SD	.189		
		MEAN 376.7200	GEOM_MEAN 2.5290	70_30RATIO	1.414	95_05RATIO	3.889					
		SKEWNESS 2.6170	GSKEW .9420	KURTOSIS	8.3410	GKURT	1.0590					
		DOSAGE Not stated			MODE_ADMIN IV							
		POPULATION 42 non-diabetic subjects and 8 relatives			SOURCE Fig. 4, p. 402							
		UNITS min? (See Diabetes 28, p. 41, 1979)										
		COMMENT Data taken from a trimodal histogram. Values represent midpoints of ranges.										
	3	CHEMICAL Hexobarbital	PARAMETER T1/2		SAMP_SIZE	29	COEF_VAR	.363	GEOM_SD	.128		
		MEAN 4.7160	GEOM_MEAN .6530	70_30RATIO	1.363	95_05RATIO	2.316					
		SKEWNESS 2.3750	GSKEW 1.0450	KURTOSIS	7.2220	GKURT	1.7580					
		DOSAGE Not stated			MODE_ADMIN Not stated							
		POPULATION 29 healthy volunteers			SOURCE Fig. 7, p. 406							
		UNITS hr										
		COMMENT Data taken from a histogram. Values represent midpoints of ranges.										
ICARTD73E0C0	1	CHEMICAL Phenylbutazone	PARAMETER T1/2		SAMP_SIZE	8	COEF_VAR	.278	GEOM_SD	.120		
		MEAN 60.2370	GEOM_MEAN 1.7650	70_30RATIO	1.242	95_05RATIO	.000					
		SKEWNESS .4330	GSKEW -.0010	KURTOSIS	-1.0690	GKURT	-1.1340					
		DOSAGE 300 mg			MODE_ADMIN 0							
		POPULATION 8 women 17-30 years			SOURCE Table 1, p.24							
		UNITS min										
		COMMENT All data used taken before start of use of oral contraceptives										
	2	CHEMICAL Antipyrine	PARAMETER T1/2		SAMP_SIZE	8	COEF_VAR	.331	GEOM_SD	.167		
		MEAN 10.5500	GEOM_MEAN .9980	70_30RATIO	1.298	95_05RATIO	.000					
		SKEWNESS -.2320	GSKEW -.7330	KURTOSIS	-1.1890	GKURT	-.8150					
		DOSAGE 1 gm			MODE_ADMIN 0							
		POPULATION 8 women 17-30 years			SOURCE Table 1, p.24							
		UNITS hr										
		COMMENT										
ICHESE82CEAN	1	CHEMICAL Theophylline	PARAMETER T1/2		SAMP_SIZE	15	COEF_VAR	.262	GEOM_SD	.120		
		MEAN 6.1500	GEOM_MEAN .7740	70_30RATIO	1.429	95_05RATIO	2.437					

IDENTITY	EXPNO										
		SKEWNESS	.0310	GSKEW	-.3450	KURTOSIS	-1.2710	GKURT	-1.0230		
		DOSAGE 300 mg					MODE_ADMIN 0				
		POPULATION 15 healthy adults, 18-28, 6 male					SOURCE T1,fig 2,pp.480,483				
		UNITS hr									
		COMMENT Mean of half-lives observed for 2 different preps									
IDIVOM82CKIV	1	CHEMICAL Clobazam		PARAMETER T1/2			SAMP_SIZE 12		COEF_VAR .539	GEOM_SD .210	
		MEAN 24.7500	GEOM_MEAN	1.3440	70_30RATIO	1.609	95_05RATIO	3.785			
		SKEWNESS .9060	GSKEW	.5530	KURTOSIS	-.8550	GKURT	-1.2740			
		DOSAGE 20 mg					MODE_ADMIN 0				
		POPULATION 12 healthy male volunteers					SOURCE fig.3, p.73				
		UNITS hr									
		COMMENT Fasting trial only									
IELLIH84TINS	1	CHEMICAL Trimazosin		PARAMETER T1/2			SAMP_SIZE 6		COEF_VAR .263	GEOM_SD .120	
		MEAN 150.6670	GEOM_MEAN	2.1650	70_30RATIO	1.557	95_05RATIO	.000			
		SKEWNESS -.1330	GSKEW	-.2190	KURTOSIS	-2.0660	GKURT	-2.0790			
		DOSAGE 200 mg					MODE_ADMIN 0				
		POPULATION Six healthy normotensive men, ages 24-39					SOURCE Table 1, p. 159				
		UNITS min									
		COMMENT									
	2	CHEMICAL Trimazosin		PARAMETER T1/2			SAMP_SIZE 6		COEF_VAR .337	GEOM_SD .147	
		MEAN 172.0000	GEOM_MEAN	2.2150	70_30RATIO	1.740	95_05RATIO	.000			
		SKEWNESS .1930	GSKEW	.0830	KURTOSIS	-2.0510	GKURT	-2.0880			
		DOSAGE 100 mg					MODE_ADMIN IV				
		POPULATION Six healthy normotensive men, ages 24-39					SOURCE Table 1, p. 159				
		UNITS min									
		COMMENT									
IFITZG79IVIK	1	CHEMICAL Norepinephrine		PARAMETER T1/2			SAMP_SIZE 5		COEF_VAR .326	GEOM_SD .139	
		MEAN 2.0900	GEOM_MEAN	.3020	70_30RATIO	1.718	95_05RATIO	.000			
		SKEWNESS .2530	GSKEW	.2070	KURTOSIS	-2.2030	GKURT	-2.1930			
		DOSAGE .005 ug/kg					MODE_ADMIN IV				
		POPULATION 5 healthy male volunteers--early 30's					SOURCE Table 3, p. 671				
		UNITS min									
		COMMENT									
IFLEUH8OPMAT	1	CHEMICAL Mefruside		PARAMETER T1/2			SAMP_SIZE 8		COEF_VAR .504	GEOM_SD .243	
		MEAN 7.3750	GEOM_MEAN	.8120	70_30RATIO	2.441	95_05RATIO	.000			
		SKEWNESS .1190	GSKEW	-.2030	KURTOSIS	-1.8410	GKURT	-1.7920			
		DOSAGE 25 or 50 mg					MODE_ADMIN 0				
		POPULATION 8 healthy human subjects					SOURCE Table 1, p. 72				
		UNITS hrs									
		COMMENT T1/2 from 2nd phase of elimination used									
IFOURJ81POTS	1	CHEMICAL Timolol		PARAMETER AUC			SAMP_SIZE 5		COEF_VAR .518	GEOM_SD .278	
		MEAN .9300	GEOM_MEAN	-.0940	70_30RATIO	2.889	95_05RATIO	.000			
		SKEWNESS -.2980	GSKEW	-.3230	KURTOSIS	-2.2340	GKURT	-2.1910			
		DOSAGE 20 mg					MODE_ADMIN 0				
		POPULATION 5 subjects, 2 women, 3 men, aged 20 and 25 years					SOURCE				
		UNITS ug/ml-hr									

IDENTITY	EXPNO											
		COMMENT		PARAMETER	Cmax	SAMP_SIZE	5	COEF_VAR	.483	GEOM_SD	.239	
		CHEMICAL	Timolol		-.5900	70_30RATIO	2.301	95_05RATIO	.000			
		MEAN	.2880	GEOM_MEAN	-.2520	KURTOSIS	-2.1120	GKURT	-2.0150			
		SKEWNESS	-.0450	GSKEW			MODE_ADMIN	0				
		DOSAGE	20 mg									
		POPULATION	5 subjects, 2 women, 3 men, aged 20 and 25 years				SOURCE					
		UNITS	(ug/ml)/(mg/kg dose)									
		COMMENT										
		CHEMICAL	Timolol	PARAMETER	T1/2	SAMP_SIZE	5	COEF_VAR	.149	GEOM_SD	.062	
		MEAN	2.6160	GEOM_MEAN	.4140	70_30RATIO	1.182	95_05RATIO	.000			
		SKEWNESS	.5350	GSKEW	.4400	KURTOSIS	-1.5710	GKURT	-1.6730			
		DOSAGE	20 mg				MODE_ADMIN	0				
		POPULATION	5 subjects, 2 women, 3 men, aged 20 and 25 years				SOURCE	Table 1, p. 195				
		UNITS	hr									
		COMMENT										
IGAILJ79PLDR	1	CHEMICAL	Lithium	PARAMETER	T1/2	SAMP_SIZE	24	COEF_VAR	.278	GEOM_SD	.118	
		MEAN	28.4750	GEOM_MEAN	1.4390	70_30RATIO	1.477	95_05RATIO	2.562			
		SKEWNESS	.5810	GSKEW	.1610	KURTOSIS	-.6450	GKURT	-1.0520			
		DOSAGE	20-36.5 mmol dose, various regimens				MODE_ADMIN	0				
		POPULATION	24 healthy volunteers, 18-63 years, 17 male				SOURCE	Table 2,pp.594-5				
		UNITS	hr									
		COMMENT	T1/2=(ln2)*(V1+V2)/u									
IGILEH81DIP*	1	CHEMICAL	Propylthiouracil	PARAMETER	T1/2	SAMP_SIZE	10	COEF_VAR	.286	GEOM_SD	.121	
		MEAN	1.3170	GEOM_MEAN	.1040	70_30RATIO	1.350	95_05RATIO	2.329			
		SKEWNESS	.5340	GSKEW	.1870	KURTOSIS	-1.0030	GKURT	-1.3490			
		DOSAGE	177-300 mg, 15 mins				MODE_ADMIN	IV				
		POPULATION	10 healthy male volunteers, 20-35 years				SOURCE	Table 1, p. 467				
		UNITS	hr									
		COMMENT										
IGRAHA79BAPC	1	CHEMICAL	Cimetidine	PARAMETER	T1/2	SAMP_SIZE	10	COEF_VAR	.555	GEOM_SD	.226	
		MEAN	2.0900	GEOM_MEAN	.2660	70_30RATIO	1.769	95_05RATIO	5.222			
		SKEWNESS	.9770	GSKEW	.2360	KURTOSIS	-.1190	GKURT	-1.2140			
		DOSAGE	100 mg				MODE_ADMIN	IV				
		POPULATION	10 volunteers, 22-25 years, 5 male				SOURCE	Table 1, p. 336				
		UNITS	hr									
		COMMENT										
	2	CHEMICAL	Cimetidine	PARAMETER	T1/2	SAMP_SIZE	10	COEF_VAR	.189	GEOM_SD	.083	
		MEAN	1.5400	GEOM_MEAN	.1800	70_30RATIO	1.307	95_05RATIO	1.666			
		SKEWNESS	.1280	GSKEW	-.0340	KURTOSIS	-1.5660	GKURT	-1.6510			
		DOSAGE	400 mg				MODE_ADMIN	0				
		POPULATION	Ten volunteers, 22-25 years, 5 male				SOURCE	Table 2, p. 337				
		UNITS	hrs									
		COMMENT	Data from table 2, p. 337									
IGUSTL84KMIC	1	CHEMICAL	Morphine	PARAMETER	T1/2	SAMP_SIZE	7	COEF_VAR	.386	GEOM_SD	.167	
		MEAN	105.7140	GEOM_MEAN	1.9970	70_30RATIO	1.761	95_05RATIO	.000			
		SKEWNESS	.3720	GSKEW	.1160	KURTOSIS	-1.6180	GKURT	-1.8270			
		DOSAGE	.05 mg/kg				MODE_ADMIN	PAR				

IDENTITY	EXPNO	
		POPULATION 7 male atheletes, 22-37 yrs, arthroscopic knee surgery.
		UNITS min SOURCE Table 3, p. 537
		COMMENT Morphine administered "epidural". Half-life measured in CSF.
IHERMP83PDAI	1	CHEMICAL Diltiazem PARAMETER T1/2 SAMP_SIZE 12 COEF_VAR .307 GEOM_SD .110
		MEAN 3.1210 GEOM_MEAN .4800 70_30RATIO 1.122 95_05RATIO 2.490
		SKEWNESS 1.7610 GSKEW 1.3060 KURTOSIS 2.2580 GKURT 1.0220
		DOSAGE 15mg, 60mg MODE_ADMIN IV and O
		POPULATION 12 volunteers, 20-26 years
		UNITS hr SOURCE Tables 2-3, p. 350
		COMMENT Data are average of trials with IV and oral dosage
IJACKD83LEFP	1	CHEMICAL Metoprolol PARAMETER T1/2 SAMP_SIZE 8 COEF_VAR .215 GEOM_SD .083
		MEAN 4.1870 GEOM_MEAN .6140 70_30RATIO 1.173 95_05RATIO .000
		SKEWNESS 1.2580 GSKEW 1.0480 KURTOSIS .2440 GKURT -.2070
		DOSAGE 100 mg MODE_ADMIN O
		POPULATION 8 young healthy volunteers
		UNITS hr SOURCE Table 1, p. 189
		COMMENT AUC data not useable--no weight correction possible.
IJOCHR82PABI	1	CHEMICAL Nitrazepam PARAMETER T1/2 SAMP_SIZE 6 COEF_VAR .088 GEOM_SD .036
		MEAN 30.4220 GEOM_MEAN 1.4820 70_30RATIO 1.062 95_05RATIO .000
		SKEWNESS 1.0370 GSKEW 1.0080 KURTOSIS -.6620 GKURT -2.3250
		DOSAGE 5 mg for all routes MODE_ADMIN IV, O, PAR
		POPULATION 7 healthy male vol. 23-27 yrs--1 excluded
		UNITS hr SOURCE T 1 & 2, pp.237-240
		COMMENT Data are means of IV, O and rectal trials for each individ.
IJOCHR83CPBA	1	CHEMICAL Brotizolam PARAMETER AUC SAMP_SIZE 8 COEF_VAR .268 GEOM_SD .110
		MEAN 452.4120 GEOM_MEAN 2.6430 70_30RATIO 1.287 95_05RATIO .000
		SKEWNESS .6930 GSKEW .3920 KURTOSIS -.9220 GKURT -1.3510
		DOSAGE .5 mg MODE_ADMIN O
		POPULATION 8 young healthy volunteers, age 21-6, 5 male
		UNITS (ng-min/ml)/(mg/kg dose) SOURCE Table 3, p. 2945
		COMMENT AUC data expressed per mg/kg dosage for each individual.
		CHEMICAL Brotizolam PARAMETER T1/2 SAMP_SIZE 8 COEF_VAR .219 GEOM_SD .105
		MEAN 5.0120 GEOM_MEAN .6900 70_30RATIO 1.334 95_05RATIO .000
		SKEWNESS -.4730 GSKEW -.6720 KURTOSIS -1.4900 GKURT -1.1260
		DOSAGE .5 mg MODE_ADMIN O
		POPULATION 8 young healthy volunteers, age 21-6, 5 male
		UNITS hr SOURCE Table 2, p. 2945
		COMMENT AUC data expressed per mg/kg dosage for each individual.
	2	CHEMICAL Triazolam PARAMETER AUC SAMP_SIZE 8 COEF_VAR .681 GEOM_SD .306
		MEAN 131.5240 GEOM_MEAN 2.0300 70_30RATIO 1.964 95_05RATIO .000
		SKEWNESS .8410 GSKEW -.0990 KURTOSIS -.4790 GKURT -1.4100
		DOSAGE .5 mg MODE_ADMIN O
		POPULATION 8 young healthy volunteers, age 21-6, 5 male
		UNITS (ng-min/ml)/(mg/kg dose) SOURCE Table 3, p. 2945
		COMMENT AUC data expressed per mg/kg dosage for each individual.
		CHEMICAL Triazolam PARAMETER T1/2 SAMP_SIZE 8 COEF_VAR .263 GEOM_SD .106
		MEAN 2.5500 GEOM_MEAN .3950 70_30RATIO 1.342 95_05RATIO .000

IDENTITY	EXPNO												
		SKEWNESS	.8090	GSKEW	.4950	KURTOSIS	-.6590	GKURT	-1.0780				
		DOSAGE .5 mg					MODE_ADMIN 0						
		POPULATION 8 young healthy volunteers, age 21-6, 5 male					SOURCE Table 2, p. 2945						
		UNITS hr											
		COMMENT AUC data expressed per mg/kg dosage for each individual.											
IKLEIC84NKAD	1	CHEMICAL Nifedipine			PARAMETER T1/2		SAMP_SIZE	6	COEF_VAR	.204	GEOM_SD	.097	
		MEAN	1.6830	GEOM_MEAN	.2180	70_30RATIO	1.168	95_05RATIO	.000				
		SKEWNESS	-.4770	GSKEW	-.7300	KURTOSIS	-1.2140	GKURT	-.9690				
		DOSAGE .015 mg/kg					MODE_ADMIN IV						
		POPULATION 6 healthy men, age 22-8					SOURCE Table I, p. 744						
		UNITS hr											
		COMMENT Data for capsules cannot be combined with data for slower-abs tablets.											
	2	CHEMICAL Nifedipine			PARAMETER Cmax		SAMP_SIZE	6	COEF_VAR	.144	GEOM_SD	.062	
		MEAN	409.4830	GEOM_MEAN	2.6090	70_30RATIO	1.140	95_05RATIO	.000				
		SKEWNESS	.1200	GSKEW	.1050	KURTOSIS	-2.1200	GKURT	-3.6290				
		DOSAGE 20 mg capsules (slow absorption)					MODE_ADMIN 0						
		POPULATION 6 healthy men, age 22-8					SOURCE Table I, p. 745						
		UNITS (ng/ml)/(mg/kg dose)											
		COMMENT Data for capsules cannot be combined with data for slower-abs tablets.											
	3	CHEMICAL Nifedipine			PARAMETER Cmax		SAMP_SIZE	6	COEF_VAR	.369	GEOM_SD	.143	
		MEAN	90.4180	GEOM_MEAN	1.9350	70_30RATIO	1.257	95_05RATIO	.000				
		SKEWNESS	.9650	GSKEW	.5520	KURTOSIS	-.5870	GKURT	-.9310				
		DOSAGE 20 mg chrystalline tablet (fast abs.)					MODE_ADMIN 0						
		POPULATION 6 healthy men, age 22-8					SOURCE Table I, p. 745						
		UNITS (ng/ml)/(mg/kg dose)											
		COMMENT Data for capsules cannot be combined with data for slower-abs tablets.											
ILIEDH85PDLB	1	CHEMICAL Dixyrazine			PARAMETER T1/2		SAMP_SIZE	8	COEF_VAR	.196	GEOM_SD	.083	
		MEAN	3.4000	GEOM_MEAN	.5240	70_30RATIO	1.265	95_05RATIO	.000				
		SKEWNESS	.4330	GSKEW	.3320	KURTOSIS	-1.6710	GKURT	-1.7540				
		DOSAGE 10 mg					MODE_ADMIN IV						
		POPULATION 8 volunteers, 21-39 yrs, dif. less than 10% from ideal wt.					SOURCE Table I, p. 90						
		UNITS hr											
		COMMENT Other T1/2 data suspicious--differs by route of admin.											
	2	CHEMICAL Dixyrazine			PARAMETER AUC		SAMP_SIZE	8	COEF_VAR	.911	GEOM_SD	.413	
		MEAN	143.8500	GEOM_MEAN	1.9940	70_30RATIO	2.819	95_05RATIO	.000				
		SKEWNESS	.7080	GSKEW	.0640	KURTOSIS	-1.4470	GKURT	-1.4340				
		DOSAGE 25 mg while fasting					MODE_ADMIN 0						
		POPULATION 8 volunteers, 21-39 yrs, dif. less than 10% from ideal wt.					SOURCE Table I, p. 90						
		UNITS (nmol-hr/l)/(mg/kg dose)											
		COMMENT All results expressed per mg/kg dosage.											
		CHEMICAL Dixyrazine			PARAMETER Cmax		SAMP_SIZE	8	COEF_VAR	.922	GEOM_SD	.406	
		MEAN	24.1010	GEOM_MEAN	1.2190	70_30RATIO	3.019	95_05RATIO	.000				
		SKEWNESS	.7470	GSKEW	.1660	KURTOSIS	-1.3450	GKURT	-1.5360				
		DOSAGE 25 mg while fasting					MODE_ADMIN 0						
		POPULATION 8 volunteers, 21-39 yrs, dif. less than 10% from ideal wt.					SOURCE Table I, p. 90						
		UNITS (nmol/l)/(mg/kg dose)											
		COMMENT All results expressed per mg/kg dosage.											

IDENTITY	EXPNO												
ILIEDH8SPDL8	3	CHEMICAL	Dixyrazine	PARAMETER	AUC	SAMP_SIZE	8	COEF_VAR	.673	GEOM_SD	.374		
		MEAN	231.9750	GEOM_MEAN	2.2490	70_30RATIO	2.668	95_05RATIO	.000				
		SKEWNESS	.1850	GSKEW	-.4630	KURTOSIS	-1.8230	GKURT	-1.2870				
		DOSAGE	25 mg after standardized breakfast				MODE_ADMIN	0					
		POPULATION	8 volunteers, 21-39 yrs, dif. less than 10% from ideal wt.				SOURCE	Table I, p. 90					
		UNITS	(nmol-hr/l)/(mg/kg dose)										
		COMMENT	All results expressed per mg/kg dosage.										
		CHEMICAL	Dixyrazine	PARAMETER	Cmax	SAMP_SIZE	8	COEF_VAR	.702	GEOM_SD	.400		
		MEAN	42.8370	GEOM_MEAN	1.4960	70_30RATIO	4.281	95_05RATIO	.000				
		SKEWNESS	-.0170	GSKEW	-.2760	KURTOSIS	-2.1090	GKURT	-1.8560				
		DOSAGE	25 mg after standardized breakfast				MODE_ADMIN	0					
		POPULATION	8 volunteers, 21-39 yrs, dif. less than 10% from ideal wt.										
		UNITS	(nmol/l)/(mg/kg dose)				SOURCE	Table I, p. 90					
		COMMENT	All results expressed per mg/kg dosage.										
ILONNG84SSKS	1	CHEMICAL	Phenylpropanolamine	PARAMETER	AUC	SAMP_SIZE	8	COEF_VAR	.250	GEOM_SD	.109		
		MEAN	929.1750	GEOM_MEAN	2.9560	70_30RATIO	1.410	95_05RATIO	.000				
		SKEWNESS	.2200	GSKEW	.0480	KURTOSIS	-1.6810	GKURT	-1.8940				
		DOSAGE	100 mg 2X/day for 3 days				MODE_ADMIN	0					
		POPULATION	8 healthy volunteers--6 male--24-56 yrs				SOURCE	Table 1, p. 40					
		UNITS	(ng-hr/ml)/(mg/kg dose)										
		COMMENT	Cmax and AUC results expressed per mg/kg body weight.										
		CHEMICAL	Phenylpropanolamine	PARAMETER	Cmax	SAMP_SIZE	8	COEF_VAR	.270	GEOM_SD	.113		
		MEAN	113.7100	GEOM_MEAN	2.0430	70_30RATIO	1.432	95_05RATIO	.000				
		SKEWNESS	.4620	GSKEW	.3180	KURTOSIS	-1.5810	GKURT	-1.8160				
		DOSAGE	100 mg 2X/day for 3 days				MODE_ADMIN	0					
		POPULATION	8 healthy volunteers--6 male--24-56 yrs				SOURCE	Table 1, p. 40					
		UNITS	(ng/ml)/(mg/kg dose)										
		COMMENT	Cmax and AUC results expressed per mg/kg body weight.										
		CHEMICAL	Phenylpropanolamine	PARAMETER	T1/2	SAMP_SIZE	7	COEF_VAR	.173	GEOM_SD	.077		
		MEAN	5.6290	GEOM_MEAN	.7450	70_30RATIO	1.158	95_05RATIO	.000				
		SKEWNESS	.0420	GSKEW	-.2090	KURTOSIS	-1.2490	GKURT	-1.3150				
		DOSAGE	100 mg 2X/day for 3 days				MODE_ADMIN	0					
		POPULATION	8 healthy volunteers--6 male--24-56 yrs				SOURCE	Table 1, p. 40					
		UNITS	hr										
		COMMENT	Cmax and AUC results expressed per mg/kg body weight.										
IMAHOC83KAMS	1	CHEMICAL	Sulfinpyrazone	PARAMETER	T1/2	SAMP_SIZE	5	COEF_VAR	.356	GEOM_SD	.142		
		MEAN	299.0000	GEOM_MEAN	2.4560	70_30RATIO	1.412	95_05RATIO	.000				
		SKEWNESS	.6820	GSKEW	.4610	KURTOSIS	-1.3780	GKURT	-1.6330				
		DOSAGE	200 mg				MODE_ADMIN	0					
		POPULATION	5 normal subjects--2 male--after 1 excluded				SOURCE	Table 1, p. 494					
		UNITS	min										
		COMMENT	One subject excluded because of technical difficulties										
IMILLC85PMIM	1	CHEMICAL	Theophylline	PARAMETER	T1/2	SAMP_SIZE	91	COEF_VAR	.213	GEOM_SD	.088		
		MEAN	7.4690	GEOM_MEAN	.8640	70_30RATIO	1.229	95_05RATIO	1.745				
		SKEWNESS	1.2130	GSKEW	.1980	KURTOSIS	3.3670	GKURT	1.1560				
		DOSAGE	5 mg/kg				MODE_ADMIN	0					
		POPULATION	79 unrelated ss's + 12 single members from pairs of twins				SOURCE	Tb 1 + Fg 2, p. 1419					
		UNITS	hr										

IDENTITY	EXPNO												
		COMMENT T1/2 values calculated from elimination rate constants.											
IMILLM84TMVA	1	CHEMICAL Theophylline		PARAMETER T1/2		SAMP_SIZE 30		COEF_VAR .365		GEOM_SD .151			
		MEAN 413.5332	GEOM_MEAN 2.5905	70_30RATIO 1.414	95_05RATIO 3.348								
		SKEWNESS .8678	GSKEW .2358	KURTOSIS .0054	GKURT -.8139								
		DOSAGE 4mg/kg			MODE_ADMIN O								
		POPULATION 1 twin from each of 24 pairs plus 6 non-twins			SOURCE Table 1, pp. 172-3								
		UNITS min											
		COMMENT											
IMITC883MDIV	1	CHEMICAL Mexiletine		PARAMETER AUC		SAMP_SIZE 5		COEF_VAR .155		GEOM_SD .070			
		MEAN 538.5000	GEOM_MEAN 2.7270	70_30RATIO 1.254	95_05RATIO .000								
		SKEWNESS -.3230	GSKEW -.3800	KURTOSIS -1.9800	GKURT -2.2680								
		DOSAGE 3 mg/kg			MODE_ADMIN IV								
		POPULATION 5 healthy fasting males, 22-34			SOURCE Table 1, p. 283								
		UNITS (ug-min/ml)											
		COMMENT All data are mean of two conditions: acid and alkaline urine.											
		CHEMICAL Mexiletine		PARAMETER T1/2		SAMP_SIZE 5		COEF_VAR .157		GEOM_SD .066			
		MEAN 8.2100	GEOM_MEAN .9100	70_30RATIO 1.071	95_05RATIO .000								
		SKEWNESS .5750	GSKEW .4220	KURTOSIS -1.3350	GKURT -1.4390								
		DOSAGE 3 mg/kg			MODE_ADMIN IV								
		POPULATION 5 healthy fasting males, 22-34			SOURCE Table 1, p. 283								
		UNITS hr											
		COMMENT All data are mean of two conditions: acid and alkaline urine.											
IMONSA79KTIR	1	CHEMICAL Tricholorethylene		PARAMETER T1/2		SAMP_SIZE 5		COEF_VAR .237		GEOM_SD .091			
		MEAN 5.4920	GEOM_MEAN .7310	70_30RATIO 1.093	95_05RATIO .000								
		SKEWNESS 1.0050	GSKEW .9660	KURTOSIS -1.0020	GKURT -1.0490								
		DOSAGE 70 ppm			MODE_ADMIN IN								
		POPULATION Five male volunteers			SOURCE Table 2, p. 285								
		UNITS hr											
		COMMENT T1/2 calculated from exhaled air conc. at 2 & 20 hrs.											
INASHR84SIVI	1	CHEMICAL Acetaminophen		PARAMETER T1/2		SAMP_SIZE 12		COEF_VAR .184		GEOM_SD .080			
		MEAN 3.7080	GEOM_MEAN .5620	70_30RATIO 1.311	95_05RATIO 1.695								
		SKEWNESS .1740	GSKEW .0350	KURTOSIS -1.6070	GKURT -1.6640								
		DOSAGE 10 mg/kg			MODE_ADMIN O								
		POPULATION 1 Twin selected randomly from each of 6 MZ and DZ pairs.			SOURCE Table 1, p. 425								
		UNITS hr											
		COMMENT											
INOGUH83PPBI	1	CHEMICAL Prifinium bromide		PARAMETER T1/2		SAMP_SIZE 6		COEF_VAR .123		GEOM_SD .054			
		MEAN 2.1570	GEOM_MEAN .3310	70_30RATIO 1.161	95_05RATIO .000								
		SKEWNESS .0970	GSKEW -.0020	KURTOSIS -1.7330	GKURT -1.7840								
		DOSAGE 60 mg, 7.5 mg			MODE_ADMIN IV, O								
		POPULATION Six healthy male volunteers, 32-50 years			SOURCE T 1-2, pp. 215-6								
		UNITS hr											
		COMMENT T1/2 data are average of oral and IV trials											
	2	CHEMICAL Prifinium bromide		PARAMETER AUC		SAMP_SIZE 6		COEF_VAR .248		GEOM_SD .109			
		MEAN 2,858.0000	GEOM_MEAN 3.4450	70_30RATIO 1.498	95_05RATIO .000								
		SKEWNESS .1230	GSKEW .0360	KURTOSIS -2.0480	GKURT -2.2290								

IDENTITY	EXPNO											
		DOSAGE 60 mg						MODE_ADMIN O				
		POPULATION Six healthy male volunteers, 32-50 years						SOURCE Table 1, p. 215				
		UNITS (ng-hr/ml)/(mg/kl dose)										
		COMMENT										
		CHEMICAL Prifinium bromide		PARAMETER Cmax		SAMP_SIZE	6	COEF_VAR	.264	GEOM_SD	.115	
		MEAN	654.6600	GEOM_MEAN	2.8030	70_30RATIO	1.400	95_05RATIO	.000			
		SKEWNESS	.2210	GSKEW	.0190	KURTOSIS	-1.7410	GKURT	-1.8760			
		DOSAGE 60 mg						MODE_ADMIN O				
		POPULATION Six healthy male volunteers, 32-50 years						SOURCE Table 1, p. 215				
		UNITS (ng/ml)/(mg/kl dose)										
		COMMENT										
INORRS83PATN	1	CHEMICAL N-Formimidoyl T		PARAMETER 1/Clear		SAMP_SIZE	11	COEF_VAR	.553	GEOM_SD	.277	
		MEAN	.0380	GEOM_MEAN	-1.4980	70_30RATIO	2.191	95_05RATIO	5.475			
		SKEWNESS	.2310	GSKEW	-.2100	KURTOSIS	-1.6960	GKURT	-1.6260			
		DOSAGE 250 mg						MODE_ADMIN O				
		POPULATION 11 healthy males, 19-28 years, after 1 excluded						SOURCE Table 3, p. 297				
		UNITS min-1.73m/ml)										
		COMMENT Renal clearance of N-Formimidoyl Theinamycin avg of 2 trials										
INYBEL84PPTI	1	CHEMICAL Terbutaline		PARAMETER T1/2		SAMP_SIZE	6	COEF_VAR	.277	GEOM_SD	.128	
		MEAN	17.8500	GEOM_MEAN	1.2360	70_30RATIO	1.556	95_05RATIO	.000			
		SKEWNESS	-.1840	GSKEW	-.2770	KURTOSIS	-2.0670	GKURT	-1.9980			
		DOSAGE 5 mg tablets given every 12 h						MODE_ADMIN O				
		POPULATION 3 men and 3 women						SOURCE Table 2, p. 155				
		UNITS hrs										
		COMMENT No weight correction possible for AUC, CMAX										
IODLIB84SSPT	1	CHEMICAL Trimethoprim		PARAMETER AUC		SAMP_SIZE	6	COEF_VAR	.237	GEOM_SD	.104	
		MEAN	14.5980	GEOM_MEAN	1.1540	70_30RATIO	1.326	95_05RATIO	.000			
		SKEWNESS	.1340	GSKEW	-.0640	KURTOSIS	-1.7640	GKURT	-1.7370			
		DOSAGE 300 mg 1X/day for 9 days.						MODE_ADMIN O				
		POPULATION 7 healthy subjects of both sexes, 26-63 yrs, exc. 1 dropout						SOURCE Table 1, p. 395				
		UNITS (ug-hr/ml)/(mg/kg dose)										
		COMMENT AUC data are averages of observations on days 8 and 9.										
		CHEMICAL Trimethoprim		PARAMETER T1/2		SAMP_SIZE	6	COEF_VAR	.222	GEOM_SD	.086	
		MEAN	10.6330	GEOM_MEAN	1.0190	70_30RATIO	1.085	95_05RATIO	.000			
		SKEWNESS	1.1580	GSKEW	1.0430	KURTOSIS	-.3870	GKURT	-.5630			
		DOSAGE 300 mg 1X/day for 9 days.						MODE_ADMIN O				
		POPULATION 7 healthy subjects of both sexes, 26-63 yrs, exc. 1 dropout						SOURCE Table 1, p. 395				
		UNITS hr										
		COMMENT AUC data are averages of observations on days 8 and 9.										
IOLSEH81SAIN	1	CHEMICAL Sulfadimidine		PARAMETER T1/2		SAMP_SIZE	152	COEF_VAR	.608	GEOM_SD	.261	
		MEAN	262.3025	GEOM_MEAN	2.3428	70_30RATIO	2.357	95_05RATIO	6.736			
		SKEWNESS	1.3796	GSKEW	-.0261	KURTOSIS	3.1348	GKURT	-.8926			
		DOSAGE 10mg/kg						MODE_ADMIN O				
		POPULATION 152 healthy drug-free Norwegians, 16-60 years, 75 male						SOURCE Fig 3, p. 121				
		UNITS min										
		COMMENT Laps had a significantly higher propostion of rapid acetylators										
IOLSS883DSSC	1	CHEMICAL Aspirin		PARAMETER Cas		SAMP_SIZE	8	COEF_VAR	.211	GEOM_SD	.088	

IDENTITY	EXPNO											
		MEAN	.0190	GEOM_MEAN	-1.7360	70_30RATIO	1.216	95_05RATIO	.000			
		SKEWNESS	.4560	GSKEW	.2750	KURTOSIS	-1.4960	GKURT	-1.6160			
		DOSAGE 3.5-4.5 g/day in 2 doses for 38 days						MODE_ADMIN	IV			
		POPULATION 8 healthy volunteers, 19-40 years						SOURCE	Table 2, p. 82			
		UNITS (mmol/l) per mg/kg dose										
		COMMENT										
IPASAF85PN**	1	CHEMICAL Nifedipine		PARAMETER T1/2		SAMP_SIZE	9	COEF_VAR	.211	GEOM_SD	.091	
		MEAN	127.3330	GEOM_MEAN	2.0960	70_30RATIO	1.386	95_05RATIO	.000			
		SKEWNESS	.2130	GSKEW	.1350	KURTOSIS	-1.8880	GKURT	-2.0970			
		DOSAGE 20 mg tablet						MODE_ADMIN	0			
		POPULATION 9 young male volunteers, 20-30 yrs						SOURCE	Table 1, p. 65			
		UNITS min										
		COMMENT Impossible to correct for body weight for other parameters.										
IPENNM81GVIR	1	CHEMICAL Antipyrine		PARAMETER T1/2		SAMP_SIZE	20	COEF_VAR	.168	GEOM_SD	.073	
		MEAN	12.4430	GEOM_MEAN	1.0890	70_30RATIO	1.215	95_05RATIO	1.758			
		SKEWNESS	.2280	GSKEW	-.0800	KURTOSIS	-.7510	GKURT	-.9420			
		DOSAGE 18 mg/kg						MODE_ADMIN	0			
		POPULATION 1 twin from each of 20 sets of MZ & DZ twins						SOURCE				
		UNITS hr										
		COMMENT One of each twin pair used, T1/2 calc. from K Elim.										
IPISAF84VAEI	1	CHEMICAL Ethosuximide		PARAMETER T1/2		SAMP_SIZE	6	COEF_VAR	.136	GEOM_SD	.061	
		MEAN	43.9830	GEOM_MEAN	1.6400	70_30RATIO	1.093	95_05RATIO	.000			
		SKEWNESS	-.2150	GSKEW	-.4260	KURTOSIS	-1.1880	GKURT	-1.3640			
		DOSAGE 500 mg						MODE_ADMIN	0			
		POPULATION 6 drug free volunteers, 4 males, 2 sisters, 18-42 yrs.						SOURCE	Table 1, p. 231			
		UNITS hr										
		COMMENT Impossible to correct for body weight for other parameters.										
IREDOA79BLCI	1	CHEMICAL Cimetidine		PARAMETER AUC		SAMP_SIZE	20	COEF_VAR	.352	GEOM_SD	.147	
		MEAN	294.8000	GEOM_MEAN	2.4450	70_30RATIO	1.587	95_05RATIO	2.779			
		SKEWNESS	.7820	GSKEW	.2430	KURTOSIS	-.0630	GKURT	-1.1590			
		DOSAGE 200 mg						MODE_ADMIN	0			
		POPULATION 20 normal healthy volunteers, 22-84 years						SOURCE				
		UNITS (mg/ml*hr)(kg body wt.)										
		COMMENT										
		CHEMICAL Cimetidine		PARAMETER T1/2		SAMP_SIZE	20	COEF_VAR	.257	GEOM_SD	.106	
		MEAN	139.0000	GEOM_MEAN	2.1300	70_30RATIO	1.316	95_05RATIO	2.226			
		SKEWNESS	.8180	GSKEW	.4470	KURTOSIS	-.3200	GKURT	-.9450			
		DOSAGE 200 mg						MODE_ADMIN	0			
		POPULATION 20 normal healthy volunteers, 22-84 years						SOURCE				
		UNITS (mg/ml*hr)(kg body wt.)										
		COMMENT										
IREITD81ATCA	1	CHEMICAL Theophylline		PARAMETER T1/2		SAMP_SIZE	6	COEF_VAR	.278	GEOM_SD	.133	
		MEAN	7.6670	GEOM_MEAN	.8690	70_30RATIO	1.332	95_05RATIO	.000			
		SKEWNESS	-.1860	GSKEW	-.5140	KURTOSIS	-1.5470	GKURT	-1.2820			
		DOSAGE 4mg/kg						MODE_ADMIN	0			
		POPULATION 6 male volunteers, 24-31 years						SOURCE	Table 1, p. 583			
		UNITS hr										

IDENTITY	EXPNO	
		COMMENT Data from control w/o interactive cimetidine.
IROLLD8OIDIA	1	CHEMICAL Amitriptyline PARAMETER T1/2 SAMP_SIZE 6 COEF_VAR .191 GEOM_SD .080
		MEAN 25.6670 GEOM_MEAN 1.4030 TO_3ORATIO 1.244 95_O5RATIO .000
		SKEWNESS .5540 GSKEW .4340 KURTOSIS -1.4920 GKURT -1.7240
		DOSAGE 50mg, 25mg MODE_ADMIN O, PAR
		POPULATION Six healthy males, 24-39 years SOURCE Table 2, pp.126-7
		UNITS hr
		COMMENT Mean T1/2 for 50 mg oral and 25 mg IM trials.
	2	CHEMICAL Nortriptyline PARAMETER T1/2 SAMP_SIZE 6 COEF_VAR .282 GEOM_SD .116
		MEAN 17.4000 GEOM_MEAN 1.4374 TO_3ORATIO 1.491 95_O5RATIO .000
		SKEWNESS .5118 GSKEW .4824 KURTOSIS -1.9645 GKURT -1.9824
		DOSAGE 57 mg MODE_ADMIN O
		POPULATION Six healthy males, 24-39 years SOURCE Table 2, p. 126
		UNITS hrs
		COMMENT
IROSSL81SDPM	1	CHEMICAL Metoclopramide PARAMETER AUC SAMP_SIZE 6 COEF_VAR .306 GEOM_SD .144
		MEAN 20.6940 GEOM_MEAN 1.2970 TO_3ORATIO 1.531 95_O5RATIO .000
		SKEWNESS -.1710 GSKEW -.3620 KURTOSIS -1.9530 GKURT -1.7180
		DOSAGE 10 mg MODE_ADMIN IV
		POPULATION 6 healthy adults, 22-39 years SOURCE Table 1, p. 467
		UNITS (mg hr/l)*kg
		COMMENT
		CHEMICAL Metoclopramide PARAMETER T1/2 SAMP_SIZE 6 COEF_VAR .176 GEOM_SD .071
		MEAN 4.5530 GEOM_MEAN .6530 TO_3ORATIO 1.062 95_O5RATIO .000
		SKEWNESS .9360 GSKEW .7490 KURTOSIS -.6190 GKURT -.7790
		DOSAGE 10 mg MODE_ADMIN IV
		POPULATION 6 healthy adults, 22-39 years SOURCE Table 1, p. 467
		UNITS hr
		COMMENT
	2	CHEMICAL Metoclopramide PARAMETER AUC SAMP_SIZE 6 COEF_VAR .411 GEOM_SD .198
		MEAN 15.9730 GEOM_MEAN 1.1680 TO_3ORATIO 1.928 95_O5RATIO .000
		SKEWNESS -.0910 GSKEW -.2530 KURTOSIS -2.0680 GKURT -1.9780
		DOSAGE 10 mg MODE_ADMIN O
		POPULATION 6 healthy adults, 22-39 years SOURCE Table 1, p. 467
		UNITS (mg hr/l)*kg
		COMMENT
		CHEMICAL Metoclopramide PARAMETER Cmax SAMP_SIZE 6 COEF_VAR .157 GEOM_SD .070
		MEAN 3.2060 GEOM_MEAN .5010 TO_3ORATIO 1.254 95_O5RATIO .000
		SKEWNESS -.2220 GSKEW -.2910 KURTOSIS -1.9550 GKURT -1.9270
		DOSAGE 10 mg MODE_ADMIN O
		POPULATION 6 healthy adults, 22-39 years SOURCE Table 1, p. 467
		UNITS (mg hr/l)*kg
		COMMENT
		CHEMICAL Metoclopramide PARAMETER T1/2 SAMP_SIZE 6 COEF_VAR .190 GEOM_SD .087
		MEAN 5.1720 GEOM_MEAN .7070 TO_3ORATIO 1.247 95_O5RATIO .000
		SKEWNESS -.2270 GSKEW -.3410 KURTOSIS -1.8010 GKURT -1.8280
		DOSAGE 10 mg MODE_ADMIN O
		POPULATION 6 healthy adults, 22-39 years

IDENTITY	EXPNO												
		UNITS (mg hr/l)*kg						SOURCE Table 1, p. 467					
		COMMENT											
ISHIVC75TVIA	1	CHEMICAL Acetaminophen		PARAMETER T1/2		SAMP_SIZE	8	COEF_VAR	.193	GEOM_SD	.081		
		MEAN	121.2560	GEOM_MEAN	2.0770	70_30RATIO	1.123	95_05RATIO	.000				
		SKEWNESS	.5460	GSKEW	.3660	KURTOSIS	-1.2860	GKURT	-1.5320				
		DOSAGE 13.9 mg/kg					MODE_ADMIN 0						
		POPULATION 8 healthy males 22-32 years					SOURCE						
		UNITS min											
		COMMENT											
	2	CHEMICAL Phenacetin		PARAMETER T1/2		SAMP_SIZE	9	COEF_VAR	.141	GEOM_SD	.058		
		MEAN	52.6890	GEOM_MEAN	1.7180	70_30RATIO	1.181	95_05RATIO	.000				
		SKEWNESS	.8090	GSKEW	.7300	KURTOSIS	-1.0950	GKURT	-1.4870				
		DOSAGE 21.4 mg/kg					MODE_ADMIN 0						
		POPULATION 9 healthy males 22-32 years					SOURCE						
		UNITS min											
		COMMENT T1/2's are averages of observations at 6am & 2pm											
ISOUBJ840ADA	1	CHEMICAL Theophylline		PARAMETER Cmax		SAMP_SIZE	7	COEF_VAR	.096	GEOM_SD	.041		
		MEAN	1.2030	GEOM_MEAN	.0790	70_30RATIO	1.126	95_05RATIO	.000				
		SKEWNESS	.2090	GSKEW	.1220	KURTOSIS	-1.6320	GKURT	-1.6480				
		DOSAGE 500mg/day for 9 days					MODE_ADMIN 0						
		POPULATION 7 healthy ss, 4 male, 24-32 yrs					SOURCE Table 1, p. 327						
		UNITS (ug/l)/(mg/kg dose)											
		COMMENT Data are average of Cmax on days 1 and 9 of experiment per mg/kg dose.											
ISOUIP79MNDK	1	CHEMICAL Sulfamethazine		PARAMETER AUC		SAMP_SIZE	5	COEF_VAR	.476	GEOM_SD	.231		
		MEAN	400.5400	GEOM_MEAN	2.5570	70_30RATIO	1.874	95_05RATIO	.000				
		SKEWNESS	.0890	GSKEW	-.2790	KURTOSIS	-1.8490	GKURT	-1.8250				
		DOSAGE 10 mg/kg					MODE_ADMIN 0						
		POPULATION 5 healthy males, 25-34 years					SOURCE Table 1, pp.174-5						
		UNITS (ug)(hr)/ml											
		COMMENT											
		CHEMICAL Sulfamethazine		PARAMETER Cmax		SAMP_SIZE	5	COEF_VAR	.280	GEOM_SD	.112		
		MEAN	41.2600	GEOM_MEAN	1.6030	70_30RATIO	1.207	95_05RATIO	.000				
		SKEWNESS	.7100	GSKEW	.5230	KURTOSIS	-1.3140	GKURT	-1.5080				
		DOSAGE 10 mg/kg					MODE_ADMIN 0						
		POPULATION 5 healthy males, 25-34 years					SOURCE Table 3, pp.176						
		UNITS ug/ml											
		COMMENT											
		CHEMICAL Sulfamethazine		PARAMETER T1/2		SAMP_SIZE	5	COEF_VAR	.245	GEOM_SD	.120		
		MEAN	5.5800	GEOM_MEAN	.7340	70_30RATIO	1.306	95_05RATIO	.000				
		SKEWNESS	-.5150	GSKEW	-.6320	KURTOSIS	-1.7450	GKURT	-1.5770				
		DOSAGE 10 mg/kg					MODE_ADMIN 0						
		POPULATION 5 healthy males, 25-34 years					SOURCE Table 1, pp.174-5						
		UNITS hr											
		COMMENT											
	2	CHEMICAL Sulfamethazine		PARAMETER AUC		SAMP_SIZE	5	COEF_VAR	.337	GEOM_SD	.186		
		MEAN	491.7200	GEOM_MEAN	2.6650	70_30RATIO	1.245	95_05RATIO	.000				
		SKEWNESS	-.6400	GSKEW	-.8560	KURTOSIS	-1.3950	GKURT	-1.1890				

IDENTITY	EXPNO	
		DOSAGE 40 mg/kg MODE_ADMIN 0
		POPULATION 5 healthy males, 25-34 years
		UNITS (ug)(hr)/ml SOURCE Table 1, pp.174-5
		COMMENT
		CHEMICAL Sulfamethazine PARAMETER Cmax SAMP_SIZE 5 COEF_VAR .189 GEOM_SD .088
		MEAN 103.8400 GEOM_MEAN 2.0100 70_30RATIO 1.262 95_05RATIO .000
		SKEWNESS -.4150 GSKEW -.4980 KURTOSIS -1.8650 GKURT -1.9030
		DOSAGE 40 mg/kg MODE_ADMIN 0
		POPULATION 5 healthy males, 25-34 years
		UNITS ug/ml SOURCE Table 3, p. 176
		COMMENT
		CHEMICAL Sulfamethazine PARAMETER T1/2 SAMP_SIZE 5 COEF_VAR .740 GEOM_SD .258
		MEAN 13.0000 GEOM_MEAN 1.0430 70_30RATIO 1.031 95_05RATIO .000
		SKEWNESS 1.0020 GSKEW .7520 KURTOSIS -.9930 GKURT -1.1830
		DOSAGE 40 mg/kg MODE_ADMIN 0
		POPULATION 5 healthy males, 25-34 years
		UNITS hr SOURCE Table 1, pp.174-5
		COMMENT
IVESEE7OGAEF	1	CHEMICAL Ethanol PARAMETER 1/Metab SAMP_SIZE 20 COEF_VAR .227 GEOM_SD .095
		MEAN 6.3690 GEOM_MEAN .7940 70_30RATIO 1.304 95_05RATIO 1.931
		SKEWNESS .5910 GSKEW .3640 KURTOSIS -1.0480 GKURT -1.2540
		DOSAGE 1 ml/kg MODE_ADMIN 0
		POPULATION One each of 14 twin pairs and 6 unrelated prisoners
		UNITS ml(hr)/mg SOURCE Table 2, p.198
		COMMENT
	2	CHEMICAL Antipyrine PARAMETER T1/2 SAMP_SIZE 6 COEF_VAR .470 GEOM_SD .170
		MEAN 15.6670 GEOM_MEAN 1.1640 70_30RATIO 1.393 95_05RATIO .000
		SKEWNESS 1.1090 GSKEW .8740 KURTOSIS -.5240 GKURT -.9210
		DOSAGE 18 ml/kg MODE_ADMIN 0
		POPULATION Six healthy male prisoners
		UNITS hr SOURCE Table 2, p.198
		COMMENT Data from before trial before ethanol exposure
IVESEE74FCIV	1	CHEMICAL Dicumarol PARAMETER T1/2 SAMP_SIZE 14 COEF_VAR .429 GEOM_SD .259
		MEAN 44.0000 GEOM_MEAN 1.5890 70_30RATIO 1.508 95_05RATIO 6.910
		SKEWNESS -.0110 GSKEW -1.4960 KURTOSIS -.8420 GKURT 2.1630
		DOSAGE MODE_ADMIN
		POPULATION 1 each of 14 twin pairs, 21-55, 6 male
		UNITS hr SOURCE Table 2, p. 141
		COMMENT
	2	CHEMICAL Antipyrine PARAMETER T1/2 SAMP_SIZE 14 COEF_VAR .239 GEOM_SD .110
		MEAN 11.2570 GEOM_MEAN 1.0390 70_30RATIO 1.235 95_05RATIO 2.168
		SKEWNESS -.0760 GSKEW -.4120 KURTOSIS -1.2240 GKURT -1.0890
		DOSAGE MODE_ADMIN
		POPULATION 1 each of 14 twin pairs, 21-55, 6 male
		UNITS hr SOURCE Table 2, p. 141
		COMMENT
	3	CHEMICAL Phenylbutazone PARAMETER T1/2 SAMP_SIZE 14 COEF_VAR .443 GEOM_SD .175

IDENTITY	EXPNO										
		MEAN	3.1640	GEOM_MEAN	.4670	70_30RATIO	1.292	95_05RATIO	4.818		
		SKEWNESS	1.5870	GSKEW	.0380	KURTOSIS	2.7420	GKURT	.6950		
		DOSAGE						MODE_ADMIN			
		POPULATION	1 each of 14 twin pairs, 21-55, 6 male					SOURCE	Table 2, p. 141		
		UNITS	hr								
		COMMENT									
	4	CHEMICAL	Antipyrine		PARAMETER	T1/2	SAMP_SIZE	8	COEF_VAR	.228	GEOM_SD .105
		MEAN	13.1250	GEOM_MEAN	1.1080	70_30RATIO	1.218	95_05RATIO	.000		
		SKEWNESS	-.0080	GSKEW	-.5040	KURTOSIS	-.8410	GKURT	-.6110		
		DOSAGE						MODE_ADMIN			
		POPULATION	1 each of 8 twin pairs--22-54 yrs--2 male					SOURCE	Table 3, p. 144		
		UNITS	hr								
		COMMENT									
IVESTR75AMIM	1	CHEMICAL	Antipyrine		PARAMETER	1/Clear	SAMP_SIZE	310	COEF_VAR	.389	GEOM_SD .154
		MEAN	.0360	GEOM_MEAN	-1.4680	70_30RATIO	1.500	95_05RATIO	3.125		
		SKEWNESS	1.5170	GSKEW	.3340	KURTOSIS	3.5340	GKURT	.0110		
		DOSAGE	1 g					MODE_ADMIN	IV		
		POPULATION	307 Healthy male subjects, age 18-92					SOURCE	Fig. 1, p. 427		
		UNITS	hr-kg/ml								
		COMMENT	Data from paper appear to contain 310 rather than 307 subjects.								
IVESTR79EAAC	1	CHEMICAL	Propranolol		PARAMETER	T1/2	SAMP_SIZE	27	COEF_VAR	.310	GEOM_SD .126
		MEAN	4.5040	GEOM_MEAN	.6350	70_30RATIO	1.200	95_05RATIO	2.826		
		SKEWNESS	1.0130	GSKEW	.3750	KURTOSIS	.4060	GKURT	-.4060		
		DOSAGE	80 mg/8 hr for 2 days					MODE_ADMIN	0		
		POPULATION	27 normal men, 21-73 years					SOURCE			
		UNITS	hrs								
		COMMENT									
IVON V83VUZB	1	CHEMICAL	Bromazepam		PARAMETER	AUC	SAMP_SIZE	10	COEF_VAR	.240	GEOM_SD .120
		MEAN	28,354.7000	GEOM_MEAN	4.4390	70_30RATIO	1.349	95_05RATIO	2.404		
		SKEWNESS	-.6100	GSKEW	-.9270	KURTOSIS	-1.0260	GKURT	-2.9810		
		DOSAGE	6 mg tablets					MODE_ADMIN	0		
		POPULATION	10 males, 18-27 yrs.					SOURCE	Table 3, p. 1701		
		UNITS	(ng-hr/ml)/(mg/kg dose)								
		COMMENT	"Test preparation"--claim for smaller interind. pharmacokin. differences.								
		CHEMICAL	Bromazepam		PARAMETER	Cmax	SAMP_SIZE	10	COEF_VAR	.172	GEOM_SD .080
		MEAN	1,040.9300	GEOM_MEAN	3.0110	70_30RATIO	1.175	95_05RATIO	1.830		
		SKEWNESS	-.4940	GSKEW	-.7000	KURTOSIS	-1.0940	GKURT	-1.4280		
		DOSAGE	6 mg tablets					MODE_ADMIN	0		
		POPULATION	10 males, 18-27 yrs.					SOURCE	Table 3, p. 1701		
		UNITS	(ng/ml)/(mg/kg dose)								
		COMMENT	"Test preparation"--claim for smaller interind. pharmacokin. differences.								
		CHEMICAL	Bromazepam		PARAMETER	T1/2	SAMP_SIZE	10	COEF_VAR	.157	GEOM_SD .075
		MEAN	18.9920	GEOM_MEAN	1.2730	70_30RATIO	1.158	95_05RATIO	1.868		
		SKEWNESS	-.6970	GSKEW	-1.0650	KURTOSIS	-.1810	GKURT	.3590		
		DOSAGE	6 mg tablets					MODE_ADMIN	0		
		POPULATION	10 males, 18-27 yrs.					SOURCE	Table 3, p. 1701		
		UNITS	hr								
		COMMENT	"Test preparation"--claim for smaller interind. pharmacokin. differences.								

IDENTITY	EXPND												
IVON V83VUZB	2	CHEMICAL Bromazepam		PARAMETER AUC		SAMP_SIZE 10		COEF_VAR .336		GEOM_SD .146			
		MEAN 24,986.2000	GEOM_MEAN 4.3760	70_30RATIO 1.439	95_05RATIO 2.785								
		SKEWNESS .4470	GSKEW .0590	KURTOSIS -1.1130	GKURT -2.4950								
		DOSAGE 6 mg tablets			MODE_ADMIN O								
		POPULATION 10 males, 18-27 yrs.			SOURCE Table 3, p. 1701								
		UNITS (ng-hr/ml)/(mg/kg dose)											
		COMMENT Commercially available "control preparation"--lrger. interin. diffs.?											
		CHEMICAL Bromazepam		PARAMETER Cmax		SAMP_SIZE 10		COEF_VAR .326		GEOM_SD .136			
		MEAN 1,166.1500	GEOM_MEAN 3.0470	70_30RATIO 1.490	95_05RATIO 2.483								
		SKEWNESS .5510	GSKEW .2950	KURTOSIS -1.3010	GKURT -1.5920								
		DOSAGE 6 mg tablets			MODE_ADMIN O								
		POPULATION 10 males, 18-27 yrs.			SOURCE Table 3, p. 1701								
		UNITS (ng/ml)/(mg/kg dose)											
		COMMENT Commercially available "control preparation"--lrger. interin. diffs.?											
		CHEMICAL Bromazepam		PARAMETER T1/2		SAMP_SIZE 10		COEF_VAR .181		GEOM_SD .065			
		MEAN 17.0690	GEOM_MEAN 1.2250	70_30RATIO 1.115	95_05RATIO 1.843								
		SKEWNESS -.4300	GSKEW -.6900	KURTOSIS -1.0190	GKURT -.8670								
		DOSAGE 6 mg tablets			MODE_ADMIN O								
		POPULATION 10 males, 18-27 yrs.			SOURCE Table 3, p. 1701								
		UNITS hr											
		COMMENT Commercially available "control preparation"--lrger. interin. diffs.?											
IWALKJ79PAAG	1	CHEMICAL Amikacin		PARAMETER T1/2		SAMP_SIZE 10		COEF_VAR .134		GEOM_SD .060			
		MEAN 1.9700	GEOM_MEAN .2910	70_30RATIO 1.162	95_05RATIO 1.533								
		SKEWNESS -.2360	GSKEW -.4200	KURTOSIS -1.2840	GKURT -1.0680								
		DOSAGE 500 mg			MODE_ADMIN IV								
		POPULATION Ten healthy volunteers, 7 men, 3 women, 22-32			SOURCE Table 2, p. 97								
		UNITS hrs											
		COMMENT											
	2	CHEMICAL Gentamicin		PARAMETER T1/2		SAMP_SIZE 10		COEF_VAR .328		GEOM_SD .139			
		MEAN 2.1300	GEOM_MEAN .3080	70_30RATIO 1.411	95_05RATIO 2.916								
		SKEWNESS .5610	GSKEW .1040	KURTOSIS -.9320	GKURT -1.1700								
		DOSAGE 120 mg			MODE_ADMIN IV								
		POPULATION Ten healthy volunteers, 7 men, 3 women, 22-32			SOURCE Table 1, p. 97								
		UNITS hrs											
		COMMENT											
IWOO*E78PACI	1	CHEMICAL Quinidine		PARAMETER T1/2		SAMP_SIZE 12		COEF_VAR .357		GEOM_SD .136			
		MEAN 7.1830	GEOM_MEAN .8350	70_30RATIO 1.291	95_05RATIO 2.599								
		SKEWNESS 1.1050	GSKEW .8270	KURTOSIS -.2320	GKURT -.8030								
		DOSAGE 5mg/kg			MODE_ADMIN IV								
		POPULATION 12 healthy young volunteers			SOURCE Fig. 4, p.468								
		UNITS hr											
		COMMENT											
IYKI-H85IBCO	1	CHEMICAL Insulin		PARAMETER 1/Clear		SAMP_SIZE 21		COEF_VAR .156		GEOM_SD .070			
		MEAN 2.2180	GEOM_MEAN .3410	70_30RATIO 1.222	95_05RATIO 1.653								
		SKEWNESS -.1550	GSKEW -.3390	KURTOSIS -1.3100	GKURT -1.2000								
		DOSAGE 40 mU/(sq. m-min)			MODE_ADMIN IV								
		POPULATION 21 normal wt. ss; 19-29 yrs; 16 male											

IDENTITY EXPNO

UNITS (sq. m-min)/ml SOURCE Fig. 2, p. 49
COMMENT Insulin dosage and clearance are expressed per surface area in this paper.